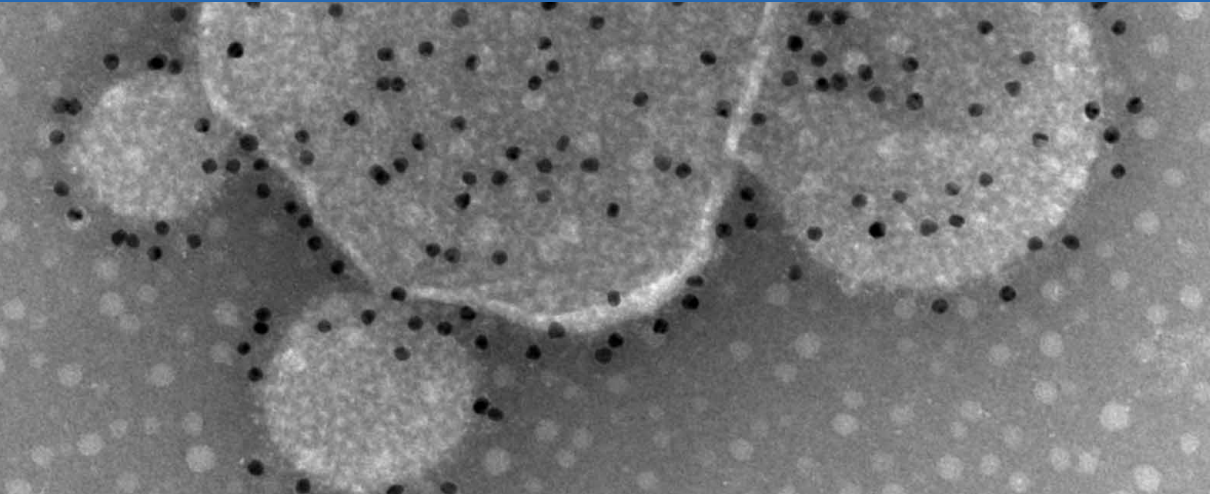
Forschungsbericht
Research Report
2017-2018

Virologisches Institut – Klinische und Molekulare Virologie



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Das Titelmotiv wurde von Dominik Damm aus der Arbeitsgruppe von Prof. Überla und von Bernd Walkenfort (Universität Duisburg-Essen) zur Verfügung gestellt. Die ektronenmikroskopischen Aufnahmen zeigen Liposome (Durchmesser: ca. 100-200 µm), auf deren Oberfläche das Hüllprotein von HIV gekoppelt ist. Die Bindung eines Gold-markierten Antikörpers (schwarze Punkte, Titelseite) und die propellerähnliche Struktur der einzelnen Hüllproteine (Rückseite) zeigen den Erhalt der natürlichen Struktur des Hüllproteins.

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UNIVERSITÄT
ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

Universitätsklinikum
Erlangen

A. Vorwort	**A. Preface**	**1**
B. Kollegium des Instituts	**B. Members of the Department**	**10**
C. Forschungsschwerpunkt Retroviren	**C. Research Focus Retroviruses**	**15**
■ Andrea Thoma-Kreß		**15**
Das Humane T-Zell-Leukämie-Virus Typ 1 (HTLV-1) und die adulte T-Zell-Leukämie	Human T-Cell Leukemia Virus Type 1 (HTLV-1) and Adult T-Cell Leukemia	
■ Ulrich Schubert		**21**
Funktion von HIV- Proteinen/ Rolle von zellulären Faktoren bei der HIV Replikation	Function of HIV Proteins/ Role of Cellular Factors in HIV Replication	
■ Thomas Gramberg		**28**
Angeborene und intrinsische Immunität in der retroviralen Infektion	Innate and Intrinsic Immunity in Retroviral Infection	
D. Forschungsschwerpunkt Herpesviren	**D. Research Focus Herpesviruses**	**33**
■ Manfred Marschall		**33**
Proteinkinasen als Regulatoren der Herpesvirus-Replikation	Protein Kinases as Regulators of Herpesviral Replication	
■ Thomas Stamminger		**43**
Genregulation des humanen Cytomegalovirus	Human Cytomegalovirus Gene Regulation	
■ Armin Ensser		**50**
Onkogene Rhadinoviren und Entdeckung von Krankheitserregern	Oncogenic Rhadinoviruses and Pathogen Discovery	
■ Brigitte Biesinger		**54**
Onkoproteine von Rhadinoviren der Primaten	Oncoproteins of Primate Rhadinoviruses	
■ Frank Neipel		**57**
Humanes Herpesvirus 8 (Kaposi Sarkom-assoziiertes Herpesvirus)	Human Herpesvirus 8 (Kaposi's Sarcoma-associated Herpesvirus)	

■ Walter Doerfler		**60**
Epigenetische Forschung	Research on Epigenetics	
E. Forschungsschwerpunkt Antvirale Immunität	**E. Research Focus Antviral Immunity**	**67**
■ Matthias Tenbusch		**67**
Gen-basierte Immunisierungsstrategien	Gene-based immunization strategies	
■ Michael Mach		**72**
Cytomegalovirus und die protektive Immunantwort	Protective Immune Response against Cytomegalovirus	
■ Klaus Überla		**77**
HIV-Impfstoff-Forschung	HIV Vaccine Research	
F. Aktivitäten in Klinischer Diagnostik	**F. Activities in Clinical Diagnostics**	**82**
■ Untersuchungsspektrum	■ Spectrum of Laboratory Tests	**83**
■ Probenaufkommen und besondere Entwicklungen	■ Trends and Particular Events in Viral Diagnostics	**86**
G. Drittmittelprojekte in der Übersicht	**G. Survey of Funded Projects**	**93**
■ Verbundforschung	■ Research Networks	**93**
■ Forschung in Einzelprojekten	■ Individual Grants	**100**
H. Publikationen	**H. Publications**	**108**
■ Beiträge zu Journalen	■ Scientific Journals	**108**
■ Kongressbeiträge	■ Abstracts	**116**
■ Buch- und Übersichtsartikel	■ Books and Reviews	**123**
■ Externe Vorträge	■ Presentations	**124**
I. Vorlesungen und Kurse	**I. Lectures and Courses**	**127**
J. Seminare und Vorträge	**J. Seminars and Workshops**	**132**
■ Seminare mit Gastsprechern	■ Seminars with Guest Speakers	**132**
■ Methoden der Molekularen Virologie	■ Methods in Molecular Virology	**138**

■ Aktuelle Themen der Klinischen Virologie	■ Current Topics in Clinical Virology	**142**
■ Vorträge im Rahmen von Promotionsprüfungen	■ Oral Presentations for Doctoral Examinations	**145**
■ Ärztliche Fortbildungsveranstaltungen	■ Continuing Medical Education	**147**
K. Dissertationen, Abschlussarbeiten	**K. Dissertations, Theses**	**152**
L. Mitgliedschaften in Gremien, Berufungen, Auszeichnungen	**L. Memberships in Boards, Appointments, Awards**	**160**
M. Finanzielle Förderung	**M. Financial Support**	**165**
■ Verbrauchsmittel	■ Supplies	**165**
■ Personalstellen	■ Personnel Positions	**166**
N. Lageplan	**N. Location**	**167**

A. Vorwort

■ Ich freue mich, Ihnen den Forschungsbericht des Virologischen Instituts für die Jahre 2017 und 2018 vorlegen zu können. Wichtige Ereignisse in diesen zwei Jahren waren sicherlich Änderungen in der Besetzung akademischer Leitungspositionen am Institut. Zum 01.02.2017 wurde Herr Prof. Matthias Tenbusch auf die W2-Professur für Gen-basierte Immunisierungsverfahren berufen. Damit wurde die Grundlagenforschung zu einer der klinisch wichtigsten Infektionserkrankungen, der Influenza, am Institut initiiert und die infektionsimmunologische Expertise des Institutes weiter gestärkt. Herr Prof. Tenbusch arbeitet an der Entwicklung eines universellen Influenza-Impfstoffes, der auf der Induktion gewebsständiger zytotoxischer T-Zellen beruht. Auch an dieser Stelle möchte ich Herrn Prof. Tenbusch mit seiner neu etablierten Arbeitsgruppe nochmal ganz herzlich willkommen heißen. Meine Gratulation gilt auch Herrn Prof. Thomas Stamminger. Er hat zum 01.01.2018 die W3-Professur für Virologie an der Universität Ulm und die Leitung des virologischen Instituts des Ulmer Universitätsklinikums angetreten. Er war seit 1995 C3-Professor am hiesigen Institut und während diesen 22 Jahren immer einer der verlässlichsten Leistungsträger. Für seinen herausragenden Einsatz möchte ich ihm, auch im Namen meines Vorgängers, Herrn Prof. Fleckenstein, ganz herzlich danken und Herrn Prof. Stamminger bei seiner neuen Tätigkeit alles Gute wünschen. Einen akademischen Meilenstein hat auch Herr Dr. Vladimir Temchura erreicht, der am 28.11.2018 seine Habilitation erfolgreich abgeschlossen hat.

■ Unser Antrag, ein Graduiertenkolleg zum Thema *Novel antiviral approaches: from small molecules to immune intervention* einzurichten, wurde im Januar 2017 sehr positiv vor Ort begutachtet, dann aber überraschend im Bewilligungsausschuss nicht zur Förderung empfohlen. Wir haben uns davon nicht entmutigen lassen und unter Berücksichtigung der konstruktiven Empfehlungen der Gutachter den Antrag in überarbeiteter Form erneut eingereicht. Die Vor-Ort-Begutachtung unter Beteiligung unserer Bostoner Kooperationspartner vom *Ragon Institute of MGH, MIT and Harvard*, Herrn Prof. Bruce Walker und Frau Prof. Sylvie LeGall, fand am 11.12.2018 statt, und wir schauen erneut gespannt auf die endgültige Entscheidung im Mai 2019. Ich möchte allen Beteiligten für die erneute Mitarbeit bei der Antragstellung danken, besonders aber Frau PD Dr. Brigitte Biesinger, die federführend den Antragsband erstellt und die Begutachtung hervorragend vorbereitet hat.

■ Einen herausragenden Erfolg im Bereich der virologischen Diagnostik konnten Herr Prof. Armin Ensser und Dr. Klaus Korn erzielen. In ihrer im *New England Journal of Medicine* publizierten Arbeit entdeckten sie mittels moderner Next Generation Sequencing-Verfahren, dass das Bornavirus auch bei gesunden Menschen tödliche Gehirnentzündungen auslösen kann.

■ Mit der Berufung in die Ständige Impfkommission (STIKO) am Robert-Koch Institut im März 2017 hat sich mir eine neue, sehr verantwortungsvolle Aufgabe gestellt, die dem Forschungsziel des Institutes, zur Entwicklung neuer Diagnose-, Therapie- oder Impfverfahren beizutragen, neue Impulse gibt und auch den Blick auf die Versorgungsforschung lenkt. Wichtige Ergebnisse dieser Gremientätigkeit waren die

Erarbeitung von Empfehlungen zur Impfung gegen die Gürtelrose und von Anwendungshinweisen zur Impfung bei Patienten mit Autoimmunerkrankungen.

■ Der Wechsel in akademischen Leitungspositionen hat auch zu einer Weiterentwicklung der Schwerpunkte der Forschungsaktivitäten des Instituts geführt. Diese liegen nun in der Erforschung molekular-virologischer Prozesse bei Infektionen mit Retroviren und Herpesviren sowie der antiviralen Immunität.

■ **Retrovirale Infektionen** sind ein zentrales Arbeitsfeld unseres Instituts. Beide humanpathogene Retroviren, das Humane T-Zell-Leukämie-Virus (HTLV) und das Humane Immundefizienzvirus (HIV), sind Gegenstand umfangreicher Forschungsarbeiten am Virologischen Institut. Die Forschungsgruppe von **Dr. Andrea Thoma-Kreß** untersucht molekulare Mechanismen der Zell-Zell-Transmission des onkogenen Retrovirus Humanes T-Zell-Leukämie-Virus Typ 1 (HTLV-1). Die Arbeitsgruppe konnte neue Messverfahren entwickeln, um die Übertragung der Viren und viraler Proteine während der Zell-Zell-Transmission einfacher und automatisiert untersuchen zu können. Die Arbeitsgruppe von **Prof. Ulrich Schubert** untersucht die Rolle von regulatorischen HIV-1 Proteinen in der Pathogenese von HIV-1, wobei gezeigt werden konnte, dass das HIV-1 p6 Gag-Protein die Membranassoziation, Ubiquitinylierung und dadurch den Eintritt der Gag-Strukturproteine in den MHC-I-Antigen-Präsentationsweg reguliert. Während Vpr bei der Entstehung des sogenannten HIV-assoziierten Lipodystrophie-Syndroms eine entscheidende Rolle spielt, vermittelt Vpu die Polyubiquitinylierung von bestimmten Wirtszellrezeptoren. Ebenfalls wurde festgestellt, dass bestimmte deubiquitinylierende Enzyme, insbesondere USP47, eine essentielle Rolle bei der HIV-1 Replikation spielen. Zufälligerweise wurde beobachtet, dass reifes p6, ein Bindungspartner von Vpr, sehr effizient von einer ubiquitären Metalloprotease, dem Insulin-degradierenden Enzym, abgebaut wird. Die Arbeitsgruppe von **Prof. Thomas Gramberg** beschäftigt sich mit der angeborenen und intrinsischen Immunität bei viralen Infektionen. Der Fokus der Gruppe liegt hierbei auf Retroviren, wie z.B. HIV-1, aber auch auf endogenen Retrotransposons, wie z.B. LINE-1 Elementen. In ihren Arbeiten untersucht die Arbeitsgruppe die Effekte der antiviralen Restriktionsfaktoren SAMHD1 und TRIM5a auf diese Pathogene. So konnte die Arbeitsgruppe beispielsweise unter Verwendung von Knockout-Mäusen die Funktion von murinem SAMHD1 *in vitro* und *in vivo* aufklären und zeigen, dass SAMHD1 eine breit gefächerte, antivirale Aktivität aufweist. In weiteren Arbeiten konnte zudem gezeigt werden, dass SAMHD1 die Retrotransposition mobiler genetischer LINE-Elemente unterbinden kann und somit ebenso zum Schutz und zur Integrität des menschlichen Genoms beiträgt. Eine von der Arbeitsgruppe von **Prof. Klaus Überla** bearbeitete Fragestellung ist, wie Intron-haltige HIV-1 mRNAs im Zellkern festgehalten werden. Ein in Kooperation mit Prof. Armin Ensser durchgeführter genomweiter Screen mittels der CRISPR/Cas-Technologie führte zur Identifizierung mehrerer Spliceosom-assoziierter Proteine. Die Inaktivierung der entsprechenden Gene erhöhte die zytoplasmatischen Spiegel der Intron-haltigen genomischen HIV-1-RNAs bis zu 140-fach. Im Bereich der Diagnostik (Leitung: Dr. Klaus Korn) steht die Entwicklung phänotypischer Resistenztests für HIV im Vordergrund.

■ **Forschungsschwerpunkt Herpesvirusinfektionen:** Das menschliche Cytomegalovirus (HCMV) ist ein Erreger von erheblicher klinischer Relevanz in der Transplantationsmedizin, der Onkologie und als Erreger pränataler Infektionen. Die Arbeitsgruppe von **Prof. Manfred**

Marschall beschäftigt sich mit der regulatorischen Rolle von Proteinkinasen bei der Replikation des humanen Cytomegalovirus und verwandten Herpesviren. Proteinkinase-Aktivitäten spielen bei dem nukleo-cytoplasmatischen Egress der viralen Partikel eine tragende Rolle. So konnte die funktionelle Beteiligung der Cytomegalovirus-kodierten Proteinkinase pUL97 an diesem Prozess demonstriert werden, sowie deren regulatorische Interaktion mit zellulären Cyclinen. Weitere virale und zelluläre Komponenten des nukleären Egress-Komplexes konnten durch Proteomics-Analysen identifiziert und funktionell charakterisiert werden. Die Beteiligung einer zellulären Prolin-cis/trans-Isomerase, Pin1, an diesen Prozessen konnte von der Arbeitsgruppe erstmals demonstriert werden. Von besonderer Wichtigkeit war der Erfolg der Röntgenstrukturaufklärung des viralen, heterodimeren Cores des Egress-Komplexes als Plattform für das Andocken und die nukleäre Freisetzung der Cytomegalovirus-Kapside. Des Weiteren zeigten die Arbeiten an Proteinkinase-Inhibitoren, aber auch an einer Serie von hochaktiven Derivaten des multipotenten Medikaments Artesunat, dass die regulatorische Wichtigkeit von Kinase-Aktivitäten und proviralen Wirtsfaktoren des Signalings einen Angriffspunkt für neue antivirale Strategien darstellt. Die Arbeitsgruppe von **Prof. Thomas Stamminger** beschäftigt sich zum einen mit der Aufklärung von immunozellulären Mechanismen, die zur Abwehr von Cytomegalovirus (CMV)-Infektionen beitragen. So gelang es vor kurzem, das zelluläre Protein SPOC1 als neuen Faktor der intrinsischen Immunabwehr zu identifizieren. Zum anderen analysiert die Gruppe virale Effektorproteine, die essenzielle Funktionen für die virale Replikation oder Dissemination ausüben. Hier fokussierten sich die Arbeiten auf den viralen, G-Protein-gekoppelten Rezeptor US27, für den eine hochregulierte Aktivierung des NF-kappa-B Signaltransduktionswegs nachgewiesen werden konnte. Die Arbeitsgruppe von **Prof. Armin Ensser** untersuchte in einer langjährigen Zusammenarbeit mit Prof. Manfred Lehner und Prof. Wolfgang Holter neuartige T-Zell-basierte Immuntherapien gegen das humane Cytomegalovirus. Bei ihrer Suche nach antiviralen Restriktionsfaktoren zeigten Dr. Florian Full und Prof. Armin Ensser, dass das centrosomale Protein TRIM43 Herpesvirusinfektionen durch die Regulierung der Integrität der Zellkern-Lamina begrenzt, und in Zusammenarbeit mit der Gruppe von Prof. Jean-Laurent Casanova fanden sie, dass der CIB1-EVER1-EVER2-Komplex die Keratinozyten-intrinsische Immunität gegen β-Papillomaviren steuert. Prof. Armin Ensser und Dr. Klaus Korn identifizierten mittels Next Generation Sequencing das Borna Disease Virus 1 (BoDV-1) im Gehirngewebe eines Patienten mit tödlicher Enzephalitis. Hierdurch wurde erstmals nachgewiesen, dass BoDV-1 tatsächlich in Menschen pathogen ist. Die Arbeitsgruppe von **PD Dr. Brigitte Biesinger** befasste sich weiterhin mit Onkoproteinen von Gamma-Herpesviren, welche humane Lymphozyten in Kultur zu permanentem Wachstum transformieren. Diese Onkoproteine interagieren mit TNF-Rezeptor-assoziierten Faktoren (TRAF). Mit deren Hilfe aktivieren sie NF-kappa-B, hemmen aber Interferon-induzierende Signalwege, wodurch sie zur viralen Persistenz beitragen könnten. Die Arbeitsgruppe von **PD Dr. Frank Neipel** befasst sich mit dem Kaposi-Sarkom-assoziierten Herpesvirus (KSHV). Die Arbeitsgruppe konnte erstmals zeigen, dass die Ephrin-Rezeptor-Tyrosinkinase A2 ein praktisch essentieller zellulärer Rezeptor für KSHV bei der Infektion endothelialer und epithelialer Zellen ist. In den Jahren 2017 und 2018 konnte die Arbeitsgruppe zeigen, dass neben EphA2 auch Integrin alpha V, nicht jedoch alpha 3, an der Infektion epithelialer Zellen durch KSHV beteiligt ist. Außerdem ergab sich, dass neben EphA2 zahlreiche weitere zelluläre Proteine durch das KSHV-RTA-Protein negativ reguliert werden. Die Arbeiten der Forschungsgruppe Epigenetik von **Prof.**

Walter Doerfler befassen sich mit den Folgen des Eindringens fremder DNA oder von Viren für die Stabilität der CpG Methylierungsprofile zellulärer DNA in Säugerzellen. Obwohl bei der Bearbeitung dieser Probleme viele Fragen noch offen sind, kann man zusammenfassend sagen, dass die chromosomale Integration fremder DNA oder die Immortalisierung von Zellen mit EBV zu Änderungen in den zellulären CpG-Methylierungsmustern führen. Diese Ergebnisse lassen die Interpretation von Daten aus Arbeiten mit genmanipulierten Zellen problematisch erscheinen. Die Klinische Diagnostik unter Leitung von **Dr. Klaus Korn** hat ein einfaches Screening-Verfahren zum Nachweis kongenitaler CMV-Infektionen bei Neugeborenen etabliert und in einer von Frau Prof. Katrin Neumann aus Bochum initiierten Studie die Prävalenz kongenitaler CMV-Infektionen in einer Kohorte von 12.000 Neugeborenen aus Deutschland und Qatar bestimmt. Die Studie zielt letztlich darauf ab, die Machbarkeit eines generellen CMV-Neugeborenen-Screenings in Deutschland aufzuzeigen und Chancen und Kosten eines solchen Screenings abzuschätzen.

■ Der Forschungsschwerpunkt **Antivirale Immunität** zielt auf ein besseres Verständnis der Kontrolle von Virusinfektionen und der Entwicklung neuer Immunisierungsverfahren ab. Die Arbeitsgruppe von **Prof. Matthias Tenbusch** entwickelt neue, gen-basierte Immunisierungsstrategien gegen virale Atemwegsinfektionen. Der Hauptfokus der Arbeit liegt in der Induktion lokaler Immunantworten an den mukosalen Eintrittspforten der Erreger. Die adenovirale Vektorimmunisierung induziert sehr potente antigen-spezifische, gewebsständige Gedächtnis-T-Zellen in der Lunge, welche einen effizienten Schutz sowohl gegen Infektionen mit einem breiten Spektrum an verschiedenen Influenza A-Viren als auch gegen das Respiratorische Synzytial-Virus vermitteln. Zudem hat die Arbeitsgruppe einen seltenen Adenovirus-Serotyp als neuen Impfvektor evaluiert, um einer möglichen Anti-Vektorimmunität in der Bevölkerung zu entgehen. Das dominante Thema im Labor von **Prof. Michael Mach** ist die Definition von Schutzmechanismen von Antikörpern gegen Cytomegaloviren. Als Modellsystem dient das murine Cytomegalovirus. Es wurden mehrere monoklonale Antikörper gegen Hüllproteine des Virus isoliert, deren *in vitro*-Neutralisationskapazität sich deutlich unterscheidet. Einige Antikörper zeigten signifikante Schutzwirkung *in vivo.* Der überraschende und neue Befund war, dass die Schutzwirkung der Antikörper vor einer Cytomegalovirus-Infektion *in vivo* nicht mit der Kapazität der Antikörper, das Virus *in vitro* zu neutralisieren, korrelierte. Es wurden eine Reihe von nicht-neutralisierenden Antikörpern gefunden, die ein ähnlich potentes Protektionspotential *in vivo* haben wie potent neutralisierende Antikörper. Über welche Mechanismen diese Antikörper schützen, ist Gegenstand der gegenwärtigen Projekte. Die Arbeitsgruppe von **Prof. Klaus Überla** untersucht Wirkmechanismen der adaptiven Immunität gegen HIV und zielt auf die Entwicklung von HIV-Impfstoffen ab. Die Arbeitsgruppe konnte zeigen, dass Antikörper gegen HIV in der Lage sind, im Tiermodell die Infektion der allerersten Zellen zu verhindern. Für die Vakzinentwicklung nutzt die Arbeitsgruppe Gen-basierte Immunisierungsverfahren, liposomale Impfstoffe, Nanopartikel und Virus-Partikel-Impfstoffe. Ein Ansatz besteht darin, T-Helfer-Zellantworten, die durch bereits zugelassene Impfstoffe induziert werden, zur Optimierung der Antikörperantwort gegen HIV zu nutzen. Mit Hilfe von B- und T-Zell-Rezeptor-transgenen Mäusen untersucht PD Dr. Vladimir Temchura darüber hinaus den Einfluss von Partikulären Impfstoffen auf die Aktivierung und Differenzierung von Antigen-spezifischen B-Zellen und follikulären T-Helfer-Zellen. Ziel der Arbeiten von Dr. Krystelle

Nganou ist es, den Einfluss der HIV-Infektion auf die durch Impfung induzierten Immunantworten zu charakterisieren.

■ Wir danken den Kollegen in der Medizinischen Fakultät und in den externen klinischen Einrichtungen sowie den niedergelassenen Kollegen in den Schwerpunkt-Praxen, mit denen wir in der Virusdiagnostik kooperieren. Unser Dank gilt den Amtsträgern im Vorstand des Universitätsklinikums und in der Universitätsleitung sowie den Mitarbeitern in der Verwaltung des Universitätsklinikums. Da mehr als neun Zehntel aller Personalkosten, Sachmittel und Investitionen unseres Instituts nach leistungsabhängigen Mechanismen bemessen sind, haben wir insbesondere den externen Drittmittelgebern zu danken. Dies sind vor allem die Deutsche Forschungsgemeinschaft, das Bundesministerium für Bildung und Forschung, die Europäische Gemeinschaft, die Kooperationspartner der Industrie und die privaten Förderer wie die Wilhelm Sander-Stiftung und die Bill & Melinda Gates-Stiftung.

Erlangen, 20.02.2019

Klaus Überla

A. Preface

■ It is my pleasure to present the research report of the Institute of Virology for the years 2017 and 2018. Important events in these two years were certainly changes in the academic leadership positions at the institute. As of February 1, 2017, Prof. Matthias Tenbusch has been appointed to the W2 Professorship for Gene-Based Immunization. Prof. Tenbusch is working on the development of an universal influenza vaccine focusing on the induction of tissue-resident T cells. He strengthens the expertise of the institute in the immunology of infectious diseases. I would like to warmly welcome Prof. Tenbusch with his newly established working group. My congratulations also go to Prof. Thomas Stamminger. On 01.01.2018 he started his position as W3-Professor for Virology at the University of Ulm and Director of the Institute for Virology at the Clinical Center of the University Ulm. He has been a C3 professor at our institute since 1995 and has always been one of the most reliable performers during these 22 years. I would like to thank Prof. Stamminger for his outstanding commitment, also on behalf of my predecessor, Prof. Fleckenstein, and sincerely wish him all the best for his new position. Dr. Vladimir Temchura, who successfully completed his habilitation on 28.11.2018, also reached an academic milestone.

■ Our proposal to set up a Research Training Group on *Novel Antiviral Approaches: from Small Molecules to Immune Intervention* was reviewed very positively on site in January 2017, but was then surprisingly not recommended for funding in the DFG Grants Committee. We did not allow ourselves to be discouraged and, in consideration of the constructive recommendations of the reviewers, re-submitted the application in revised form. The on-site evaluation with the participation of our Boston cooperation partners from the *Ragon Institute of MGH, MIT and Harvard*, Prof. Bruce Walker and Prof. Sylvie LeGall, took place on 11.12.2018, and we eagerly await the final decision in May 2019. I would like to thank all those involved for their cooperation in the application process, particularly PD Dr. Brigitte Biesinger, who excellently prepared the grant application and the on-site evaluation.

■ An outstanding success in the field of virological diagnostics was achieved by Prof. Armin Ensser and Dr. Klaus Korn. In their paper, published in the *New England Journal of Medicine*, they discovered by modern Next-Generation Sequencing methods that Borna disease virus can lead to lethal encephalitis in previously healthy people.

■ With the appointment to the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute in March 2017 I have been assigned with a new and exciting task that will also give new impetus to the institute's research goal of developing new methods for diagnosis, therapy or vaccination and will also draw attention to clinical research. Important results of this panel work were the development of guidelines for vaccination against shingles in Germany and general recommendations for vaccination of patients with autoimmune diseases.

■ The change in academic leadership positions has also shaped the research foci of the institute which are now entitled Molecular Virology of Retroviruses, Molecular Virology of Herpesviruses, and Antiviral Immunity.

■ **Molecular Virology of Retroviruses** represents a central scientific field of our Department. Both human pathogenic retroviruses, human T-cell leukemia virus (HTLV) and human immunodeficiency virus (HIV), are the subject of extensive research by the institute. The research group of **Dr. Andrea Thoma-Kreß** investigates cell-to-cell transmission of the oncogenic retrovirus Human T-cell leukemia virus Type 1 (HTLV-1). The group developed new assays and methods to facilitate studies on viral transmission and the transport of viral proteins during cell-to-cell transmission. The research group of **Prof. Ulrich Schubert** investigates the role of regulatory HIV-1 proteins in the pathogenesis of HIV-1, whereby it could be shown that the HIV-1 p6 Gag protein regulates the membrane association, ubiquitination, and thus the entry of Gag into the MHC-I antigen presentation pathway. While Vpr is involved in HIV-associated fat metabolism diseases, Vpu directs the polyubiquitination of certain host cell-receptors. Moreover, it was ascertained that certain deubiquitinating enzymes, especially USP47, play an essential role in the HIV-1 replication cycle. Serendipitously, it was observed that mature p6, a binding partner of Vpr, is very efficiently degraded by the ubiquitous metalloprotease insulin degrading enzyme. The group of **Prof. Thomas Gramberg** analyzes innate and intrinsic immune mechanisms against viral infections. The working group focuses on HIV-1 and on endogenous retrotransposons, such as LINE-1. Within their studies, the group characterizes the antiviral mechanisms of the host restriction factors SAMHD1 and TRIM5a on the replication of these pathogens. Using knockout mice the Gramberg laboratory was able to characterize the function of murine SAMHD1 *in vitro* and *in vivo.* In addition, the laboratory found that SAMHD1 blocks the replication of mobile genetic elements like LINE-1 elements and is therefore also protecting the genome and contributing to genome integrity. One of the questions addressed in **Prof. Klaus Überla's** research group is how intron-containing HIV-1 mRNAs are captured in the cell nucleus. In cooperation with Prof. Armin Ensser, a genome-wide screen using the CRISPR/Cas technology led to the identification of several spliceosome-associated proteins. The inactivation of the corresponding genes increased the cytoplasmic levels of the intron-containing genomic HIV-1 RNA up to 140-fold. In the field of diagnostics, the focus is on the development of phenotypic drug resistance tests for HIV-1.

■ The institute is also focusing on the **Molecular Virology of Herpes viruses.** The research group of **Prof. Manfred Marschall** studies the regulatory role of protein kinases in the replication of the human cytomegalovirus (HCMV) and related herpesviruses. In particular, the importance of protein kinases for the nucleo-cytoplasmic egress of viral particles has been demonstrated. A functional involvement of the cytomegalovirus-encoded protein kinase pUL97 in these processes was shown, as well as their regulatory interaction with cellular cyclins. Further viral and cellular components of the nuclear egress complex were identified by the use of proteomics approaches and were functionally characterized. Our studies demonstrated for the first time the involvement of a cellular prolyl cis/trans isomerase, Pin1, in these processes. Particular importance had the x-ray-based resolution of the crystal structure of the nuclear egress core heterodimer as a docking site and functional platform for the nuclear release of cytomegaloviral capsids. Moreover, an investigation of the antiviral potential of protein kinase inhibitors, but also a series of highly active derivates of the multipotent drug artesunate, illustrated that these kinase activities, and similarly those of proviral host factors of signaling pathways, can be exploited as promising targets for future antiviral strategies. The group of **Prof. Thomas Stamminger** investigates immunocellular

mechanisms that contribute to the defense against cytomegalovirus (CMV) infections. During the last two years they could identify the cellular protein SPOC1 as a novel factor that mediates intrinsic immunity against CMV. Furthermore, viral effector proteins are characterized which play essential roles during HCMV replication or dissemination. The group also demonstrated that the viral G-protein coupled receptor pUS27 is able to induce a highly regulated activation of the NF-kappa-B signal transduction pathway. In a long standing cooperation with Prof. Manfred Lehner and Prof. Wolfgang Holter, the group of **Prof. Armin Ensser** investigated novel T-cell based immunotherapies for human cytomegalovirus. In their search for antiviral restriction factors, Dr. Florian Full and Prof. Armin Ensser demonstrated that the centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity and, in cooperation with the group of Prof. Jean-Laurent Casanova, showed that human CIB1–EVER1–EVER2 complex governs keratinocyte-intrinsic immunity to β-papillomaviruses. Using an unbiased next-generation sequencing approach, Dr. Klaus Korn and Prof. Armin Ensser also detected Borna disease virus 1 (BoDV-1) in brain tissue of a patient with fatal encephalitis, demonstrating that BoDV-1 is indeed pathogenic in humans. The group of **PD Dr. Brigitte Biesinger** continued to investigate oncoproteins of gamma herpesviruses that are capable to transform human lymphocytes to permanent growth in culture. Their oncoproteins interact with TNF receptor-associated factors (TRAF) to activate NF-kappa-B, but also to inhibit interferon-inducing signaling pathways. Thereby, the viral oncoproteins may contribute to viral persistence. The laboratory of **PD Dr. Frank Neipel** is studying the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV). The group could show for the first time that the Ephrin receptor tyrosinkinase A2 (EphA2) is an essential receptor for KSHV upon infection of endothelial and epithelial cells. The group could show in 2017 and 2018 that, in addition to EphA2, integrein alpha V, but not alpha 3, contributes to the infection of epithelial cells by KSHV. Furthermore, in addition to EphA2 numerous cellular proteins are negatively regulated by KSHV RTA-protein. The Epigenetics Group of **Prof. Walter Doerfler** has continued their research on the epigenetic consequences of foreign DNA or of virus particle intrusions into mammalian cells. While many questions remain, the available evidence obtained from a number of different biological systems supports the view that the genomic integration of foreign DNA or the immortalization of cells with EBV can lead to alterations in the cells' CpG methylation profiles. These findings call for a caveat towards the interpretation of data obtained from genetically manipulated cells. The Clinical Diagnostics section under the direction of **Dr. Klaus Korn** has established a simple screening procedure for the detection of congenital CMV infections in newborns, and has determined the prevalence of congenital CMV infections in a cohort of 12,000 newborns from Germany and Qatar in a study initiated by Prof. Katrin Neumann from Bochum. The study ultimately aims to demonstrate the feasibility of a general CMV neonatal screening in Germany and to estimate the chances and costs of such a screening.

■ In the research focus **Antiviral Immunity**, the research group of **Prof. Matthias Tenbusch** is developing novel gene-based immunization strategies against viral respiratory tract infections. A major focus of their work is the induction of local immune responses at the mucosal entry sides of the pathogens. Their adenoviral vector immunizations induce very potent antigen-specific, tissue resident memory T-cells in the lung which mediate efficient protection against infections with a broad spectrum of divergent influenza A viruses as well

as against the respiratory syncytial virus. Furthermore, the group evaluated a rare adenovirus serotype as novel viral vector vaccine to circumvent pre-existing anti-vector immunity in the human population. The lab of **Prof. Michael Mach** has continued their efforts in isolating and defining protective antibodies against cytomegalovirus. As a model system the murine cytomegalovirus is used. A number of monoclonal antibodies directed at viral envelope glycoproteins was isolated. The antibodies had vastly different capacities to neutralize the virus *in vitro*. A fraction of antibodies was capable of complete protection from infection *in vivo*. Interestingly, the *in vivo* capacity to protect from cytomegalovirus infection was not directly correlated to the *in vitro* neutralizing activity. A number of non-neutralizing antibodies could be defined which had similar protective capacity as potent neutralizing antibodies. The mechanism(s) by which these antibodies protect is a current focus of the lab. The research group of **Prof. Klaus Überla** investigates mechanisms of adaptive immunity against HIV and aims at the development of HIV vaccines. The group was able to show in a highly relevant animal model that antibodies against HIV are able to prevent the infection of the very first cells. For vaccine development, the group uses gene-based immunization methods, liposomal vaccines, nanoparticles and virus particle vaccines. One approach is to exploit T helper cell responses induced by already approved vaccines to optimize the antibody response to the HIV Env protein. Using B- and T-cell receptor transgenic mice, PD Dr. Vladimir Temchura also investigated the influence of particulate vaccines on the activation and differentiation of antigen-specific B-cells and follicular T helper cells. The aim of the work of Dr. Krystelle Nganou is to characterize the influence of HIV infection on vaccine-induced immune responses.

■ We wish to thank all friends and colleagues in our Medical School, in external clinical departments, and all colleagues in practice with whom we could cooperate in clinical virus diagnostics. We thank the members of the executive group of the University hospital, the ruling board of the University and all members in administration of the academic hospital. Since more than ninety percent of all resources for personnel, supplies and equipment are obtained by competitive funding mechanisms, we must thank the external funding institutions. Those were the German Science Foundation DFG, the Federal Ministry for Education and Research, the European Union, the cooperation partners in industry, and private supporters such as the Wilhelm Sander Foundation and the Bill & Melinda Gates Foundation.

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Human T-Cell Leukemia Virus Type 1 (HTLV-1) and Adult T-Cell Leukemia

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■ **Pathogenesis of HTLV-1.** Infections account for approximately 15-20% of human cancers. Human T-cell leukemia virus type 1 (HTLV-1), the only retrovirus causing cancer in humans, infects at least 5-10 mio. people worldwide and is the trigger for incurable neoplastic or inflammatory diseases. The viral Tax-1 (Tax) oncoprotein, a key player in initiating malignant transformation of infected $CD4^+$ T-cells, deregulates cellular signaling pathways. Upon infection of T-cells, integrated HTLV-1 persists as a provirus *in vivo*. After a latency period, which may last up to decades, HTLV-1 may cause an aggressive and highly infiltrative leukemia of $CD4^+$ T-cells, adult T-cell leukemia/lymphoma (ATL). Additionally, HTLV-1 is also the

etiologic agent of the neurologic disorder, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 persists lifelong in the presence of an active immune system. The virus has little cytotoxic effect on T-cells, but changes their growth properties. In contrast to normal T-cells, HTLV-1-infected lymphocytes can proliferate permanently in the absence of antigen stimulation and are resistant to apoptosis-inducing signals.

■ **Transmission of HTLV-1.** HTLV-1 is transmitted via breast-feeding, sexual contacts or direct exposure to HTLV-1-infected blood cells. After infection of its target cells, primarily $CD4^+$ T-cells, HTLV-1 is reversely transcribed and integrates into the host cell genome. Transmission of HTLV-1 to other cells is strictly dependent on cell-cell contacts, and cell-free infection is very inefficient. Viral particles are transferred to other cells after polarized budding at a tight, confined cell-cell contact, the so-called virological synapse. Further, viruses are transmitted via viral biofilms at virological synapses. The viral biofilms consist of an agglomeration of viruses that are packaged on top of the infected cells in a biofilm-like structure. Beyond the transmission at tight cell-cell-contacts, HTLV-1 is supposed to be transferred to other cells via long-distance connections.

■ **Tax and p8.** Two viral proteins have been shown to play a major role in virus transmission, Tax and p8. The regulatory protein Tax is the viral transactivator and also the major oncoprotein of HTLV-1. Tax not only enhances viral gene expression, but it also potently activates several cellular signaling pathways, amongst them cAMP-response element binding (CREB), nuclear factor kappa B (NF-κB), and the serum response factor pathway. Thus, Tax is a potent regulator of cellular gene expression, which contributes to viral pathogenesis and oncogenesis. Beyond, Tax has typical properties of an oncoprotein, since (1) Tax immortalizes primary rodent fibroblasts, (2) Tax induces leukemia and neurofibromas in transgenic mice, and (3) Tax initiates immortalization of primary human T lymphocytes. In late stages of HTLV-1-pathogenesis, however, Tax protein is barely detectable or only expressed in single cells in bursts and supposed to be no longer required to maintain the transformed phenotype. Since Tax is evoking a strong cytotoxic T-cell (CTL) response *in vivo*, silencing of Tax is an efficient strategy of immune evasion.

Therapeutic approaches have tried to reactivate Tax expression to enhance the CTL response, and thus, to eliminate virus-infected cells. Next to its role in initiating cellular transformation, Tax plays an essential role in remodeling of the host cell cytoskeleton during viral transmission at the virological synapse. Contrary, the accessory protein p8 induces cellular protrusions and is transferred to other cells to foster HTLV-1 cell-to-cell transmission. Thus far, detailed molecular mechanisms of HTLV-1 cell-to-cell transmission and the transfer of p8 are largely unknown.

■ **Our major research aims** are addressed by the following questions:

(1) How do the viral proteins Tax and p8 modulate the host cell to allow efficient cell-to-cell transmission of HTLV-1?

(2) How does HTLV-1 promote its own gene expression, and how can viral gene expression be manipulated?

■ **Modulation of HTLV-1-transmission by Tax.** The viral protein Tax and polarization of the host cell cytoskeleton are crucial for formation of the virological synapse, however, only little is known about the link between Tax and remodeling of the cytoskeleton to foster viral spread. Substantial insights into the different routes of HTLV-1-transmission have mainly been obtained by imaging techniques or by flow cytometry. Recently, strategies to quantify infection events with HTLV-1 improved.

We use different quantitative methods to measure virus transmission in our laboratory. The methods are based on measuring gene activity of luciferase with a cost-saving in-house luciferase assay. First, we established a reporter Jurkat T-cell line carrying a *luciferase* gene under the control of the HTLV-1 core promoter *U3R*. Upon co-culture with chronically HTLV-1-infected T-cell lines, reporter cells are infected, and upon expression of the viral transactivator Tax, the viral promoter is activated resulting in enhanced luciferase activity. However, this assay does not exclude cell fusion as the mechanism allowing intracellular Tax-dependent activation of *luciferase* gene expression. Therefore, we make use of a second method, the single-cycle replication-dependent reporter system developed by Mazurov et al. (PLoS Pathog 6:e1000788, 2010) that allows quantitation of HTLV-1 infection in co-cultured cells. Combined use of both methods facilitates quantitation of HTLV-1 transmission and already helped to unravel pathways required for cell-to-cell transmission on a quantitative basis. We could recently show that HTLV-1 usurps the host cell factor Fascin to foster virus release and cell-to-cell transmission. Fascin is an actin-bundling protein, which has evolved as a therapeutic target in several types of cancer. We previously identified Fascin as a novel target gene of Tax and also characterized the transcriptional regulation of Fascin in more detail. Since Fascin is important for the stability of actin-filaments, we asked whether it contributes to HTLV-1 transmission. Using the above mentioned quantitative techniques to measure HTLV-1 transmission, we found that repression of endogenous Fascin by short hairpin RNAs and by Fascin-specific nanobodies impaired both gag p19 release and cell-to-cell transmission in 293T cells. In Jurkat T-cells, expression of Tax led to induction of Fascin expression, and this resulted in enhanced virus release and cell-to-cell transmission to Raji/CD4$^+$ B-cells, which was reduced upon repression of Fascin. Analysis of chronically HTLV-1-infected T-cells revealed that repression of Fascin diminished virus release and gag p19 transfer to co-cultured T-cells. Spotting the mechanism, flow cytometry and automatic image analysis uncovered that Tax-induced T-cell conjugate formation occurred Fascin-independently. However, adhesion of HTLV-1-infected MT-2 cells in co-culture with Jurkat T-cells was reduced upon knockdown of Fascin. This suggests that Fascin contributes to dissemination of infected T-cells. Confocal imaging analysis of chronically infected MS-9 T-cells in co-culture with Jurkat T-cells revealed that Fascin's localization at tight cell-cell contacts is accompanied by gag polarization, suggesting that Fascin directly affects the distribution of gag to budding sites, and therefore, indirectly viral transmission. In detail, we found gag clusters that are interspersed with Fascin clusters, suggesting that Fascin makes room for gag in viral biofilms. Moreover, we observed short, Fascin-containing membrane extensions surrounding gag clusters and clutching uninfected T-cells. Finally, we detected Fascin and gag in long-distance cellular protrusions. Thus, Fascin is an interesting novel target to counteract infections with HTLV-1.

■ **Modulation of HTLV-1-transmission by p8 and transport of p8 between cells.** The HTLV-1 p8 protein is a cleavage product of the accessory p12 protein, and both p12 and p8 are thought to contribute to efficient viral persistence. Mechanistically, p8 increases the number and the length of cellular, actin-dependent protrusions among T-cells. The latter are considered to facilitate transfer of p8 to target cells and virus transmission. In the target cell, p8 is supposed to induce T-cell anergy by decreasing T-cell receptor signaling. Transfer of p8 between p8-expressing T-cells and recipient cells has been analyzed by immunofluorescence and live imaging. Since automatic quantitation of p8-transfer between cells had not been studied, we

developed a novel method allowing time saving quantitation of p8 transfer between cells by flow cytometry. After establishing a protocol for the detection of intracellular p8 by flow cytometry and validation of p8 protein expression by western blot and immunofluorescence, we set up a co-culture assay between p8-expressing donor Jurkat T-cells and recipient Jurkat T-cells that had been prestained with the well-retained live cell dye CMAC-Blue (Figure 1A). Upon quantitating the amount of p8 positive recipient cells with regard to the percentage of p8 expressing donor cells, we performed

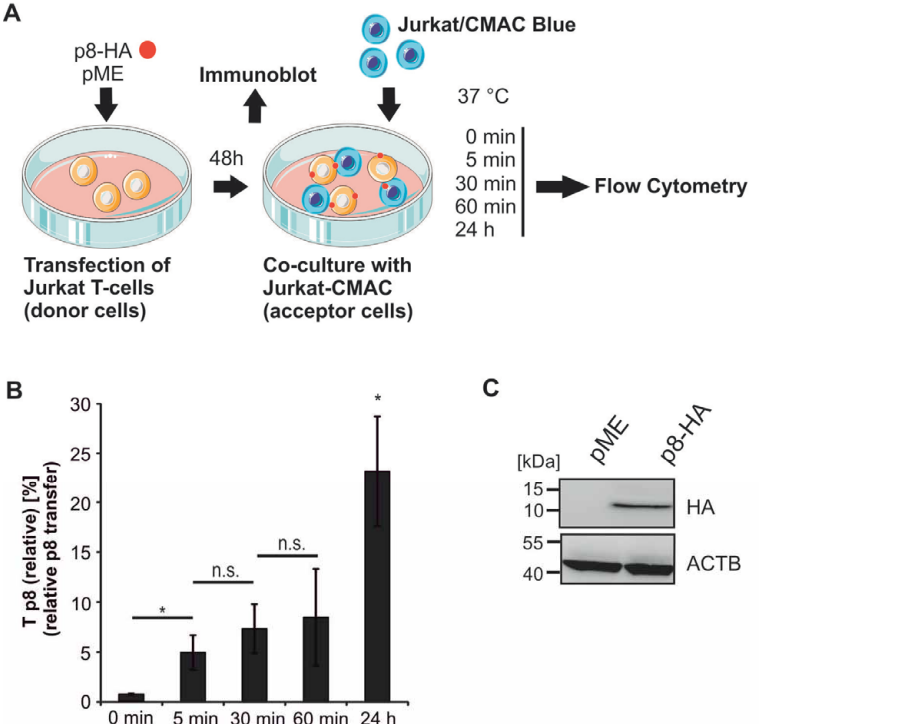

Figure 1. Detection of rapid p8 transfer between Jurkat T-cells by flow cytometry. (A) Jurkat T-cells were transfected with p8-HA expression plasmids or the control plasmid pME for 48h. Transfected p8-donor or control (pME) cells were either subjected to western blot analysis or co-cultured with equal amounts of Jurkat acceptor cells ($1*10^6$) that had been prestained with Cell Tracker Blue CMAC Dye (Jurkat-CMAC). At different time points post co-culture at 37°C (0 min, 5 min, 30 min, 60 min, 24 h), cells were fixed in 2% paraformaldehyde (PFA), permeabilized, stained and analyzed by flow cytometry. **(B)** Time course analysis of T p8(relative) as measured by flow cytometry. The means of 3-4 independent experiments +/- SE are shown and were compared as indicated using a paired t-test. * indicates $p<0.05$; n.s., not significant. **(C)** Representative western blot of p8-HA expression in Jurkat T-cells at 48 h post transfection. ACTB (β-Actin) served as housekeeping gene. *Taken from (modified):* Donhauser et al., Front. Microbiol. (2018).

time course experiments, which confirmed that p8 is rapidly transferred between Jurkat T-cells (Figure 1B). We found that p8 enters approximately 5% of recipient T-cells immediately upon co-culture for 5 min. Prolonged co-culture for up to 24 h revealed an increase of relative p8 transfer to approximately 23% of the recipient cells (Figure 1B). Western blot analysis of p8 (Figure 1C), immunofluorescence analysis of co-culture experiments and manual quantitation of p8 expression in fluorescence images confirmed the validity of the flow cytometry based assay.

Application of our novel assay revealed that manipulation of actin polymerization significantly decreased p8 transfer between Jurkat T-cells suggesting an important role of actin dynamics contributing to p8 transfer. Further, transfer of p8 was cell type dependent. Contrary to co-cultures of Jurkat T-cells, p8 transfer could hardly been detected in co-cultures of 293T donor cells with Jurkat acceptor cells. In summary, our novel assay allows rapid and automatic quantitation of p8 transfer to target cells and might thus contribute to a better understanding of cellular processes and dynamics regulating p8 transfer and HTLV-1 transmission.

■ **A novel positive feedback loop in viral oncogenesis.** It has been known for years that constitutive activation of the classical and alternative NF-κB signaling pathways by Tax is a hallmark of HTLV-1-driven cancer. NF-κB-deficient Tax transgenic mice lack the induction of ATL-associated aggressive skin diseases. Further, animal studies therapeutically targeting NF-κB slow down and reduce tumor growth in ATL-like diseases. Although there are different reports whether NF-κB is critical for initiating cellular transformation, there is a strong connection between Tax, NF-κB, tumor formation and maintenance. Having found, against expectation, that activation of NF-κB signaling specifically enhances the abundance of Tax protein (Figure 2A), but not of *Tax* transcripts, we hypothesize that Tax establishes a novel positive feedback loop between itself and NF-κB activity, which results in enhanced protein expression of Tax and might thus serve as a novel therapeutic target to interfere with Tax-driven transformation (Figure 2B). To study the impact of NF-κB activity on Tax expression in primary T-cells, we optimized in collaboration with Dr. Ciminale (Padova, Italy) a transfection protocol for primary T-cells using an approach based on the electroporation of *in vitro*-transcribed RNA. Our results showed that the RNA transfection technique combines high transfection efficiencies with low toxicity in primary T-cells. Together, these findings suggest that RNA electroporation is preferable for experiments aimed at investigating the role of HTLV-1 gene products in the context of primary T-cells, which represent the main target of HTLV-1 *in vivo*.

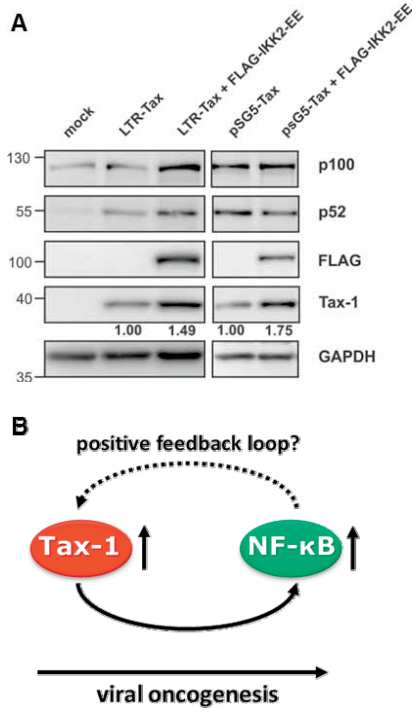

Figure 2. Identification of a putative positive feedback loop between Tax and NF-κB activity. (A) Jurkat T-cells were transfected with Tax-expression constructs (30µg each) either driven by the viral promoter (LTR-Tax) or by the SV40 promoter (pSG5-Tax). A constitutive active mutant of IKK-β, FLAG-tagged IKK2-EE (40µg), was co-transfected. After 48 h, cells were lysed and western blots detecting Tax, the NF-κB precursor p100, the cleaved p52, FLAG and the housekeeping gene GAPDH were performed. Numbers indicate Tax protein expression normalized on GAPDH. **(B)** Working model. Tax-induced NF-κB activity may result in a positive feedback loop to enhance Tax protein abundance. This feedback loop might foster viral oncogenesis.

Collaborations

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Function of HIV Proteins/ Role of Cellular Factors in HIV Replication

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- With the aim of developing new strategies in antiviral therapy and vaccination as well as the investigation of the role of the regulatory HIV-1 proteins p6, Vpr, and Vpu in the pathogenesis of HIV-1, our work has been based upon interdisciplinary cooperation and application of a broad spectrum of methods within the fields of retrovirology, molecular and cell biology, biochemistry, protein structure determination, as well as immunology. The overall research goal is to contribute to the development of novel anti-retroviral strategies by deciphering the structural constraints and molecular mechanisms governing the function of viral proteins and their cellular counterparts.

We are currently working on the following main research topics:

■ **The HIV-1 p6 Gag-protein regulates the membrane association, polyubiquitination and entry of Gag into the MHC-I pathway.** This major project focuses on the role of the HIV-1 p6 protein as part of the Gag precursor in the late processes of virus replication, especially assembly and budding.

Viruses like HIV-1 hijack a cellular system known as the endosomal sorting complex required for transport (ESCRT) in order to promote their release from the cell surface. This cellular machinery is involved in cytokinesis and in the vacuolar protein sorting of endocytosed plasma membrane proteins by regulating the abscission of membrane stalks.

The HIV-1 p6 Gag-protein regulates the final abscission step of nascent virions from the cell membrane by the action of its two late (L)-domains. Although p6 originates from one of the most polymorphic regions of the HIV-1 *gag* gene, the 52 amino acid peptide binds to at least two cellular budding factors of the ESCRT-complex, Tsg101 (tumor susceptibility gene product 101) and ALIX (ALG-2 interacting protein X), *via* its highly conserved primary PTAP and secondary YPXnL L-domains, respectively. Moreover, p6 is substrate for phosphorylation, ubiquitination and sumoylation, and mediates the incorporation of the HIV-1 accessory protein Vpr into viral particles. As expected, known functional domains mostly overlap with several conserved residues in p6. We investigated the importance of the highly conserved serine residue at position 40 (S40) which is phosphorylated by the atypical phosphokinase C (aPKC) and was until now not assigned to any known function of p6.

By performing membrane flotation assays we found that in HIV-1 expressing cells the mutant S40F, but not the conservative mutation of S40 to Asp (S40D) or Asn (S40N), leads to an increased membrane association of Gag. This correlates with an enhanced Gag-ubiquitination which predominantly consists of K48-linked polyubiquitin chains. Consistently, the S40F mutation augments the entry of Gag into the UPS and thus enhances its MHC-I antigen presentation and Gag-mediated T-cell activation. Others could show that the membrane resident ubiquitin E3 ligase Cul7 is able to ubiquitinate Gag. This finding led us to the hypothesis that the S40F mutant might also be ubiquitinated by this or other E3 ligases due to prolonged membrane association.

As an explanation for the enhanced membrane association of Gag, we found by performing high resolution NMR analysis that S40F, together with Tyr-36, induces the formation of a hydrophobic patch within the C-terminal α-helix of p6 which might account for the augmentation in membrane association of Gag.

We further analyzed the role of p6 in membrane association and found that the mutation of the highly conserved glutamic acids within p6 to alanine (E0A), like the S40F mutant, leads to an enhanced polyubiquitination and subsequent entry of Gag into the UPS and thus an increased MHC-I antigen presentation of Gag derived epitopes. In addition, like for the S40F mutant, the CA-SP1 processing of the E0A mutant is impaired, also resulting in loss of infectivity and significantly decreased replication capacity. Furthermore, the E0A mutant displays defective virus release that could not be rescued by ALIX overexpression. Most strikingly, the E0A mutant exhibits elevated membrane association which might be due to removal of the negatively charged Glu residues. We hypothesized that in *wt* situation these negative charges might contribute to the repulsion of p6 from the plasma membrane. To verify this hypothesis, we created mutants where all glutamic acids within p6 were exchanged with Asp residues (E0D)

that altered the side chain of the amino acid but maintained the overall charge of p6. Intriguingly, this mutant behaves like the *wt* in terms of ubiquitination, MHC-I antigen presentation and membrane association of Gag, leading to the assumption that the negative charges but not the nature of the side chains of the glutamic acids are important for the functionality of p6 during late steps of replication.

The cumulative data support a model in which p6, in addition to matrix, acts as a membrane targeting domain of Gag, either by hydrophobic (S40F) or electrostatic (E0A) interactions with the inner leaflet of the plasma membrane.

■ **Proteolysis of mature HIV-1 p6 Gag-protein by the insulin-degrading enzyme (IDE).** There is a significantly higher risk for type II diabetes in HIV-1 carriers, albeit the molecular mechanism for this HIV-related pathology remains enigmatic. The HIV-1 p6 Gag-protein is synthesized as the C-terminal part of the Gag polyprotein Pr55. In this context, p6 promotes virus release by its two L-domains, and facilitates the incorporation of the viral accessory protein Vpr. However, the function of p6 in its mature form, after proteolytic release from Gag, has not been investigated yet and was another main project in our lab.

We found that mature p6 represents the first known viral substrate of the ubiquitously expressed cytosolic metallo-endopeptidase insulin-degrading enzyme (IDE). IDE is sufficient and required for degradation of p6, and p6 is approximately 100-fold more efficiently degraded by IDE than its eponymous substrate insulin. This observation appears to be specific for HIV-1, as p6 proteins from HIV-2 and simian immunodeficiency virus, as well as the 51 amino acid p9 from equine infectious anaemia virus were insensitive to IDE degradation. The amount of virus-associated p6, as well as the efficiency of release and maturation of progeny viruses, does not depend on the presence of IDE in the host cells, as it was shown by CRISPR/Cas9 edited IDE KO cells. However, HIV-1 mutants harboring IDE insensitive p6 variants exhibit reduced virus replication capacity, a phenomenon that seems to depend on the presence of an X4-tropic Env. Furthermore, competing for IDE by exogenous insulin or inhibiting IDE by the highly specific inhibitor 6bK, also reduced virus replication. This effect could be specifically attributed to IDE since replication of HIV-1 variants coding for an IDE-insensitive p6 were inert towards IDE-inhibition.
Our cumulative data support a model in which removal of p6 by IDE during viral entry is important for virus replication, at least in the case of X4 tropic HIV-1.

However, it remains unclear to which extent the IDE mediated degradation is phylogenetically conserved among HIV-1. We analyzed this issue and found two HIV-1 isolates with IDE resistant p6 proteins. Sequence comparison allowed deducing one single amino acid regulating IDE sensitivity of p6. Exchange of the N-terminal leucine residue of p6 derived from the IDE sensitive isolate HIV-1_{NL4-3} with proline enhances its stability, while replacing Pro-1 of p6 from the IDE insensitive isolate SG3 with leucine restores susceptibility towards IDE. Phylogenetic analyses of this natural polymorphism revealed that the N-terminal leucine is characteristic for p6 derived from HIV-1 group M except for subtype A, which predominantly expresses p6 with an N-terminal proline. Accordingly, p6 peptides derived from subtype A are not degraded by IDE.

In conclusion, IDE mediated degradation of p6 is specific for HIV-1 group M isolates and not occasionally distributed among HIV-1.

■ **Inhibitors of deubiquitinating enzymes block HIV-1 replication and augment the presentation of Gag-derived MHC-I epitopes.** In recent years it has been well established that two major constituent parts

of the UPS – the proteasome holoenzyme and a number of ubiquitin ligases – play a crucial role, not only in virus replication but also in the regulation of the immunogenicity of HIV-1. However, the role in HIV-1 replication of the third major UPS component, the deubiquitinating enzymes (DUBs), has remained largely unknown. Thus, we studied in another project the role of DUBs in HIV-1 replication.

We could show that the DUB-inhibitors (DIs) P22077 and PR-619, specific for the DUBs USP7 and USP47, impair Gag processing and thereby reduce the infectivity of released virions without affecting viral protease activity. Furthermore, the replication capacity of X4- and R5-tropic HIV-1_{NL4-3} in human lymphatic tissue is decreased upon treatment with these inhibitors without affecting cell viability. Most strikingly, combinatory treatment with DIs and proteasome inhibitors synergistically blocks virus replication at concentrations where mono-treatment was ineffective, indicating that DIs can boost the anti-retroviral activity of proteasome inhibitors. In addition, P22077 and PR-619 increase the polyubiquitination of Gag and thus its entry into the UPS and MHC-I pathway.

In summary, our data point towards a model in which specific inhibitors of DUBs not only interfere with virus spread but also increase the immune recognition of HIV-1 expressing cells. Thus, DIs might offer multiple options in antiretroviral therapy.

■ **Function of regulatory virus proteins in the pathogenesis of HIV-1.** Deciphering the molecular mechanism of small regulatory virus proteins provides knowledge about specific host-virus interactions and should open the path to the development of innovative antiviral strategies. The major focus of this long term project in cooperation with the lab of Dr. Ashok Balasubramanyam (Baylor College of Medicine, Houston, TX, USA) has been the functional characterization of the HIV-1 accessory protein Vpr. In addition we performed functional analysis of another HIV-1 accessory protein, Vpu.

■ **The lentiviral protein R (Vpr).** In the last years, we intensively investigated the HIV-1 accessory protein Vpr (viral protein R) of HIV-1. The 96 amino acid Vpr has multiple functions in HIV-1 pathogenesis, including virion incorporation, nuclear translocation of the HIV-1 preintegration complex, induction of cell cycle arrest at the G2/M phase, and the regulation of apoptosis.

HIV patients manifest adipose dysfunction characterized by accelerated lipolysis, hepatosteatosis, dyslipidemia, insulin resistance, and hyperglycemia. However, the *in vivo* mechanisms whereby HIV infection induces those defects in human adipose disorders have not been reported. Thus, in cooperation with the lab of Dr. Ashok Balasubramanyam the pathogenic role of Vpr in HIV-associated adipose dysfunction was investigated. It could be shown that Vpr released from HIV-1 in tissue reservoirs, can disrupt PPAR/GR (peroxisome proliferator-activated receptor/ glucocorticoid receptor) co-regulation and cell cycle control to produce adipose dysfunction and hepatosteatosis. Moreover, we could show that Vpr broadly altered hepatic expression of LXR (liver X receptor) α-regulated lipid metabolic genes. Furthermore, Vpr diminishes hepatic fatty acid ß-oxidation which altogether contributes to the HIV-associated fatty liver disease.

Confirmation of these mechanisms in patients could pave the way for targeted treatment with small-molecule inhibitors of Vpr, GR antagonists, or PPAR agonists.

■ **The lentiviral protein U (Vpu).** The HIV-1 accessory protein Vpu is an 81-amino-acid oligomeric type 1 integral membrane phosphoprotein, which is encoded exclusively in HIV-1 and related simian immunodeficiency viruses (SIV), but

not in HIV-2. Vpu has been shown to induce degradation of the CD4 receptor by the ER-associated protein degradation (ERAD) pathway and to enhance virus particle release from the plasma membrane. Randomization of the transmembrane (TM) domain prevents Vpu`s ion channel formation and impairs its ability to regulate virus release. This suggested a causal relation between the ion channel activity of Vpu and its augmentation of virus release. Recently, it was shown that Vpu enhances HIV-1 virion release by counteracting a cellular restriction factor termed CD317 (also known as tetherin, BST-2 or HM1.24). Thus, in order to analyze whether ion channel activity of Vpu correlates with viral particle release, several TM mutants were generated. The highly conserved residues Ala-14 and Ala-18 in the TM domain of Vpu were analyzed for their ability to form ion channels and to counteract CD317.

Mutation of Ala-14 and Ala-18 to asparagine impairs the efficiency of surface down-regulation of CD317. However, both mutants still exhibit ion channel activity in 293T cells, indicating that channel activity of Vpu is not sufficient to support virus release. Furthermore, to assess its relevance in CD317 counteraction, we mutated Ser-23, which is essential for Vpu's ion channel activity, to alanine (S23A). Intriguingly, the S23A mutant still efficiently interacts with CD317, and thus supports virus release in the presence of CD317. Taken together, our data suggest that the ion channel activity of Vpu is not critical for counteraction of CD317.

Moreover, it was shown that Vpu also induces downregulation of the coactivating NK cell receptor, the NK, T-cell, B-cell antigen (NTB-A), from the cell surface in order to evade lysis of HIV-1 infected cells by NK cells. Pulse-chase analyses revealed that HIV-1 Vpu affects the glycosylation pattern of NTB-A by a mechanism that is distinct from the Vpu induced downregulation of CD4 and tetherin. In the presence of Vpu, only the high mannose form of NTB-A was detectable, suggesting that Vpu prevented the formation of the mature form of NTB-A. This phenomenon is associated with the ability of Vpu to downregulate cell surface NTB-A by retention of NTB-A within the Golgi-compartment. Furthermore, the Vpu-mediated effect on NTB-A glycosylation is highly conserved among Vpu proteins derived from HIV-1 and SIV and corresponds to the level of downregulation of NTB-A. Together, our results suggest that the reduction of NTB-A from the cell surface is associated with the Vpu-mediated effect on the glycosylation pattern of newly synthesized NTB-A molecules.

Moreover, it was shown that Vpu induces downregulation of cell surface CD155, a ligand for the DNAM-1 activating receptor of NK and $CD8^+$ T-cells, to evade NK cell-mediated immune response. In order to analyze the effect of Vpu on the surface expression of CD155, Vpu TM and cytoplasmic deletion mutants were analyzed in HeLa cells, which constitutively express endogenous CD155. The results suggested that the TM domain of Vpu, particularly Ala-10, Ala-14 and Ala-18, is crucial for cell surface downregulation of CD155. Moreover, Vpu induces accumulation of CD155 in perinuclear compartments indicating that Vpu might inhibit trafficking of CD155 to the cell surface. Thus, Vpu seems to subvert NK cell responses against HIV-1 infected T-cells by modulation of multiple receptors necessary for NK cell activation.

Collaborations

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- ImmunoLogik GmbH, Berlin

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Innate and Intrinsic Immunity in Retroviral Infection

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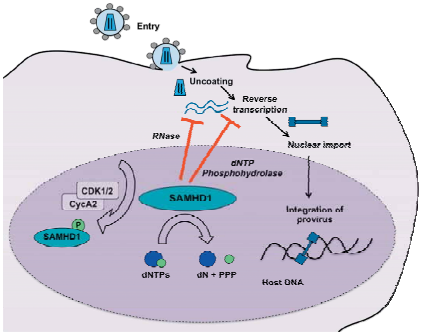
■ For efficient replication within a host cell viruses have to circumvent several intrinsic barriers. This includes avoiding being recognized or sensed by the host cell and to counteract or evade intrinsic antiviral mechanisms within the cell. To counteract intrinsic immunity, lentiviruses like HIV-1, have evolved specialized accessory proteins that are essential for viral replication *in vivo* and have been shown to counteract innate immune mechanisms. The major focus of our research is to understand how innate immune mechanisms restrict retroviral replication and analyzing the role of lentiviral accessory proteins in counteracting cellular defense mechanisms. Also, we are interested in understanding how intrinsic immune factors sense and signal during viral replication and by which means the induced responses and restrictions are counteracted by viruses.

In addition to exogenous retroviruses, we are also including endogenous retroviruses and retroelements in our studies to analyze the role of restriction factors, like SAMHD1, or innate sensing molecules on the replication of mobile genetic elements. Comparing the replication of exogenous viruses with their endogenous "cousins" in light of intrinsic restriction and immune sensing will further contribute to a better understanding of antiviral innate immune mechanisms, autoimmunity, and genome stability of the host.

■ **The antiretroviral restriction factor SAMHD1.** Viruses of the HIV-2/SIVsm lineage encode the accessory protein Vpx. While Vpx is not required for virus replication in activated T-cells, it facilitates the infection of myeloid target cells, like macrophages and dendritic cells. In these cells, Vpx has been shown to neutralize the antiviral activity of the restriction factor SAMHD1. Mutations in SAMHD1 are known to cause the Aicardi-Goutieres syndrome (AGS) in humans. AGS is a hereditary autoimmune disease caused by an immune response to accumulating intracellular nucleic acids. SAMHD1 has been shown to act as a dNTP triphosphohydrolase and it has been suggested that SAMHD1 inhibits retroviral reverse transcription by depleting the intracellular dNTP pool. We were part of a study showing for the first time that SAMHD1 restricts infection by hydrolyzing intracellular deoxynucleoside triphosphates (dNTPs) in primary cells, thereby lowering their concentrations below those required for retroviral DNA synthesis. In addition, we also contributed to the finding that SAMHD1 is not only active in myeloid cells, but also in resting $CD4^+$ T-cells, which are known to be highly resistant to productive HIV-1 infection. Furthermore, we found that not only HIV and SIV are blocked by SAMHD1, but many diverse retroviruses belonging to the alpha-, beta-, and gamma-retrovirus genera are affected by the SAMHD1-mediated block to reverse transcription.

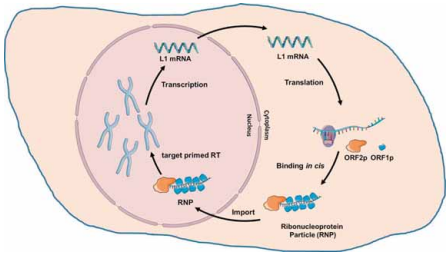


The proposed mechanisms of the SAMHD1-mediated HIV-1 restriction. Upon entry of HIV-1 into myeloid cells or resting $CD4^+$ T-cells, SAMHD1 blocks viral replication early during the viral lifecycle at or prior to reverse transcription. The dNTP hydrolase activity of SAMHD1 depletes the intracellular dNTP pool below the level required for reverse transcription. Alternatively, SAMHD1 may directly target incoming viral genomic RNA for degradation. In cycling cells, the antiviral activity of SAMHD1 is inactivated by phosphorylation at threonine 592 by CDK1/2 and Cyclin A2. The phosphorylation at T592 is lost in resting cells, activating the SAMHD1-mediated block to infection in a cell-cycle dependent manner.

■ **Analyzing the function of SAMHD1 *in vivo* using knockout mice.** To determine the role of SAMHD1 *in vivo*, we analyzed SAMHD1 knockout mice. In these mice we found that also mouse SAMHD1 reduces cellular dNTP concentrations and restricts retroviral replication in lymphocytes, macrophages, and dendritic cells *in vitro* and *in vivo*. Importantly, the absence of SAMHD1 triggered an IFN-dependent transcriptional upregulation of type I IFN-inducible genes in various cell types. A finding that is indicative of a spontaneous IFN production in SAMHD1 knockout mice. Therefore, SAMHD1-deficient mice may be serving as model system to identify the mechanisms that trigger pathogenic type I IFN responses and to analyze the mechanism how SAMHD1 restricts viral infection.

We used the SAMHD1 knockout mice to analyze the mechanism and the regulation of SAMHD1 in greater detail. We found that, similar to the human protein, the antiviral activity of murine SAMHD1 is also regulated by phosphorylation. This phosphorylation takes place at a threonine residue with a CDK1 binding site, is cell-cycle-dependent, and correlates negatively with the antiviral activity of SAMHD1. Since the exact mechanism of SAMHD1 restriction is still not completely understood, we compared the effect of the dNTP hydrolase activity and the proposed RNase activity of SAMHD1 on retroviral infection. However, we did not observe an effect of SAMHD1 on incoming viral RNA suggesting that the recently suggested RNase activity of SAMHD1 is less important for restriction.

■ **SAMHD1 inhibits the replication of endogenous retroelements.**



Model of replication of endogenous LINE-1 retroelements. Upon transcription, LINE-1 RNA is exported into the cytoplasm. LINE-1 RNA encodes two main open reading frames, ORF1p and ORF2p. While ORF1p has nucleic acid binding and chaperone activity, ORF2p encodes a reverse transcriptase (RT) and an endonuclease (EN) activity. ORF1p and ORF2p bind LINE-1 RNA in cis to form ribonucleoprotein particles (RNPs). LINE-1 RNPs enter the nucleus, most likely during mitosis, and target genomic DNA. New copies are inserted into the host genome by target primed reverse transcription mediated by the EN and RT activity of ORF2p.

The accumulation of intracellular nucleic acids derived from endogenous retroelements thriving in the absence of SAMHD1 has been discussed as potential trigger of the autoimmune disease AGS. Long interspersed element 1 (LINE-1) is the only autonomously active retrotransposon in humans and about 17% of the genome is derived from LINE1 sequences. Novel LINE-1 retrotransposition events can destabilize genome integrity and cause disease by insertional mutagenesis, insertion of splice sites, recombination, transcriptional activation of nearby genes, or by the activation of non-autonomous short interspersed elements (SINEs), like Alu elements. To this date, novel L1-mediated retrotransposition events have been identified as the disease-causing mutations in more than 120 patients.

We showed *in vitro* that SAMHD1 indeed inhibits the replication of L1 and other endogenous retroelements in cycling cells. By applying GFP- and neomycin-based reporter assays we found also the anti-L1 activity of SAMHD1 to be regulated by phosphorylation at T592. Similar to the block of HIV, the cofactor binding site and the enzymatic active HD domain of SAMHD1 proofed to be essential for restriction of L1 elements. Interestingly, phosphorylation at T592 did not correlate with the dNTP hydrolase activity of SAMHD1 in cycling 293T cells suggesting an alternative but similar mechanism of regulation. Our results suggest that SAMHD1 is important for maintaining genome integrity and support the idea of an enhanced replication of endogenous retroelements in the absence of SAMHD1 *in vivo*, potentially triggering autoimmune diseases like AGS.

■ **The antiretroviral activity of members of the TRIM protein family.** Another cellular restriction to retroviral infection is mediated by TRIM5α, one of over 70 members of the tripartite motif (TRIM) protein family. It mediates intracellular immunity against a variety of retroviruses in a species-specific manner. Of particular interest, TRIM5α of rhesus macaques

potently blocks HIV-1 infection, whereas the human protein is not active against HIV-1. The antiviral function of many closely related TRIM proteins is still ill-described. It has been shown that the expression of many TRIM proteins can be upregulated by type I interferon, which hints towards a possible function as antiviral protein. We are therefore also interested in discovering and characterizing the antiretroviral properties of different members of the TRIM protein family.

Collaborations

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D. Forschungsschwerpunkt Herpesviren
Research Focus Herpesviruses

Protein Kinases as Regulators of Herpesviral Replication

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■ **Introduction.** Human cytomegalovirus (HCMV) is a major opportunistic pathogen of humans with a worldwide distribution. Primary infection with HCMV in persons with a normal immune system is generally mild or asymptomatic, while in immunocompromised persons and in the situation of congenital infection, HCMV frequently causes systemic disease with severe clinical consequences. Most of the currently available anti-HCMV drugs face limitations in terms of unwarranted side-effects and the induction of drug resistance. Thus, the development of novel anti-HCMV drugs, and similarly also broader acting antiherpesviral drugs, is urgently required. For this, protein kinase inhibitors proved to be highly interesting drug candidates, as both cellular and herpesviral protein kinases

represent important determinants of viral replication and pathogenicity.

■ **The research concept of the group is focused on the following topics:**

■ Functional and structural characterization of the protein kinase pUL97 of HCMV
■ Cross-talk between herpesviral and cellular kinases
- nuclear egress of HCMV and other herpesviruses
- mutual interregulation between pUL97 and CDKs/cyclins
- HCMV-induced signaling, pathogenesis and host tropism

■ Protein kinase inhibitors as a new type of antiviral drugs.

■ **Functional analysis of the cytomegaloviral protein kinase pUL97.** Herpesviral protein kinases are important determinants of the efficiency of viral replication. They fulfill a number of regulatory functions by phosphorylating both viral and cellular proteins. pUL97 of HCMV is the prototype of the UL-subfamily of serine/threonine-specific herpesviral protein kinases (HvUL kinases). An analysis of the structure-activity relationship of pUL97 and homologous kinases of other herpesviruses resulted in the definition of the kinase domain, the mapping of functionally important regions and the identification of phosphorylated substrates. Experimental settings to reveal the 3D structure of pUL97 are presently performed, including both approaches of structural biology and bioinformatics. As an important functional feature of pUL97, we demonstrated that this kinase is expressed in three isoforms arising from alternative translational initiation. Catalytic activity, including autophosphorylation and substrate phosphorylation, proved to be indistinguishable for two of the isoforms (M1 and M74), while its third isoform (M157) comprised functional differences. In particular, the interaction and phosphorylation of viral substrate proteins was less efficiently performed by the smallest isoform M157. These findings could be substantiated by the analysis of recombinant HCMVs expressing individual pUL97 isoforms.

■ **The regulatory importance of protein kinases for cytomegalovirus nuclear egress.** The role of pUL97 within the HCMV replication cycle is manifested on several different stages, including viral DNA synthesis, phosphorylation-mediated inactivation of the cell cycle regulator Rb and nuclear viral capsid egress. Concerning the nuclear capsid egress, we were able to demonstrate an involvement of pUL97 in the phosphorylation of nuclear lamins. The nuclear lamina is a rigid proteinaceous meshwork underlining the inner nuclear membrane. During infection with herpesviruses, the nuclear lamina restricts the efficiency of nucleocytoplasmic transport of viral capsids, because of the large size of herpesviral capsids which does not allow a direct transition through the nuclear pore complex. Lamina destabilization requires site-specific phosphorylation of lamins and lamin-binding membrane proteins. In case of HCMV, we demonstrated that pUL97 is recruited to the nuclear lamina through the interaction with a cellular multi-ligand binding protein, p32/gC1qR, which is also associated with the lamin B receptor. pUL97 is able to phosphorylate lamins in a site-specific manner (Ser22) and to induce a morphological alteration of the nuclear lamina. Thus, pUL97 has a crucial effect on the destabilization of the lamina which is a prerequisite for the viral nuclear egress. In addition to pUL97, two other viral proteins are strictly associated with the nuclear lamina, namely pUL50 and pUL53. The pUL50-pUL53 interactor pair is considered as the core of the HCMV-specific nuclear egress complex (NEC) that contains a number of additional viral and cellular proteins. Importantly, the Ser22-specific lamin phosphorylation generates a binding motif for the cellular prolin-specific

isomerase Pin1 that induces a *cis/trans* isomerization of Pro23 in lamin A/C. This activity is highly suggestive to represent the main mechanism of the herpesvirus-induced structural conversion of the nuclear lamina thus leading to local lamina disassembly as a prerequisite for viral nuclear capsid egress (Figure 1).

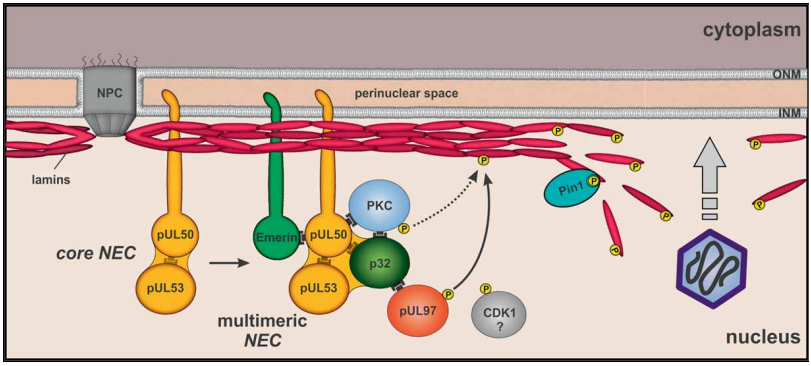


Figure 1. Schematic model of the constitution and function of the cytomegaloviral nuclear egress complex (NEC). For details see Milbradt et al., 2004 and 2016.

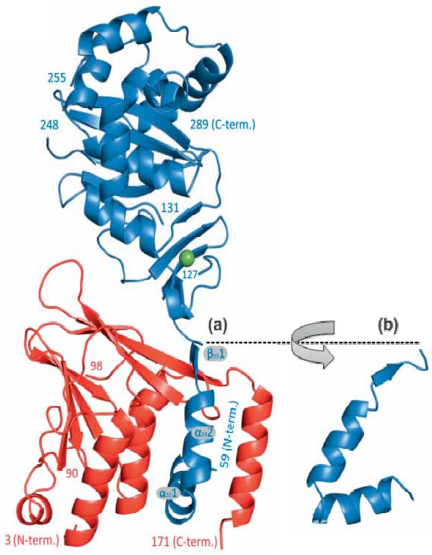


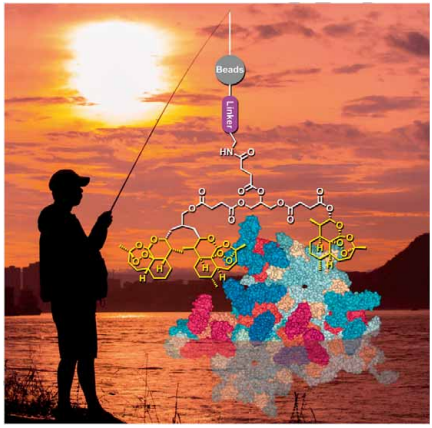
Figure 2. Crystal structure of the HCMV core NEC (heterodimeric complex pUL50-pUL53). The secondary structure elements of the hook-like N-terminal extension of pUL53 is presented in two different orientations (a) and (b), thus embracing pUL50 and becoming buried in the interface formed by three pUL50 α-helices (ribbon representation: pUL50, red; pUL53, blue). For details see Walzer et al., 2015.

Moreover, we were able to characterize the pUL50-pUL53 nuclear import and heterodimerization at the inner nuclear membrane. While pUL50 is a trans-membrane protein, directly inserted into the inner nuclear membrane, pUL53 is translocated to the nucleus via its recently mapped N-terminal NLS and is recruited to the inner nuclear rim by binding to pUL50. Thus, direct pUL50-pUL53 interaction is a prerequisite for intracellular trafficking and the fine-localization of both proteins. A hallmark of these investigations was the successful crystallization and resolution of the 3D structure of the globular domains of the pUL50-pUL53 core NEC of HCMV and other herpesviruses by our group and other investigators. The pUL53-specific features include a zinc-binding site and a hook-like N-terminal extension, the latter representing a crucial element of the pUL50-pUL53 interaction. The hook-like extension (amino acids 59–87) embraces pUL50 and contributes 1510 Å2 to the total interface area (hook-into-the-groove interaction; Figure 2). The pUL50 structure reveals a considerable repositioning of its alpha-C helix upon pUL53 binding. A close examination of the crystal structure indicated partial assembly of pUL50-pUL53

heterodimers to hexameric ring-like structures possibly providing additional scaffolding opportunities for the multimeric NEC. Our biochemical and proteomic investigations of binding partners of the pUL50-pUL53 complex suggested a combination of viral and cellular constituents associated with the multimeric NEC in its final composition at late times of HCMV replication. In particular for pUL50, five binding partners could be identified, i.e. pUL53, PKCα, p32/gC1qR, emerin and CDK1. A phospho-specific mass spectrometry analysis led to the identification of 14 major and minor sites of pUL50 phosphorylation (as putative sites for the pUL50-phosphorylating kinases pUL97, PKCα and CDK1). These are currently investigated by mutagenesis and the transfer of mutant versions of ORF-UL50 into recombinant HCMVs. The ongoing functional investigation of the HCMV-specific NEC may reveal novel insights into these pronounced functional ties of virus-host interaction.

■ **Cytomegalovirus-specific cellular signaling.** It is an established concept that cytomegalovirus infection (or similarly infections with many other human herpesviruses) induce a cellular program of signaling that is characterized by the induced expression and activity of a variety of cellular protein kinases. This kind of upregulated signaling program provides a finger print, individually reflecting the parameters of replication and pathogenesis of a single virus (virus-specific cellular signaling, VSS). In case of HCMV, we established a novel approach of kinome profiling that suggests an important role of specific cellular protein kinases for viral replication. Experimental inhibition of such kinases showed a significant reduction, whereas inhibition of other kinases led to an activation of HCMV replication. Furthermore, analysis of the mode of action of those kinase inhibitors exerting antiviral activity (VSS inhibitors) suggested a substantial benefit for the efficiency of viral replication at the immediate early or early-late phases of HCMV gene expression. Interestingly, an ongoing comparative analysis of kinase patterns induced by various herpesviruses (as representatives of the alpha-, beta- and gamma-herpesvirus subfamilies) indicated partly conserved events of kinase/signaling upregulation and, for other kinases, virus-specific differences. Thus, our combined data provide new information on host cell kinases involved in viral replication and uncovered potential targets for future diagnostic or antiviral proceedings. The latter aspect is also addressed by our long-term analysis of the antiviral mode of activity of the broad antiinfective drug artesunate. Recent findings demonstrated an important point of the antiviral activity of artesunate in that it interferes with NF-κB-specific signaling. A direct binding of artesunate to NF-κB p65 is strongly suggested by our data. Notably, the enhanced anti-HCMV activity of synthetic artesunate dimers, trimers and hybrid molecules (cooperation with the group of Svetlana B. Tsogoeva) currently opens promising novel perspectives, not only in antiviral research, but also in the mechanistic analysis of HCMV specific cellular signaling. A mass spectrometry-based proteomic approach, using linker-coupled versions of artesunate compounds (Figure 3A), revealed a selection of highly interesting drug target proteins, in particular including mitochondrial regulators. Importantly, the antiviral efficacy of artesunate compounds increased with the degree of multimerization (Figure 3B; trimers>dimers>monomers). The functional validation of these proteins is currently performed, specifically taking into account a postulated regulatory link between mitochondrial activity and the efficiency of HCMV replication.

(A)



(B)

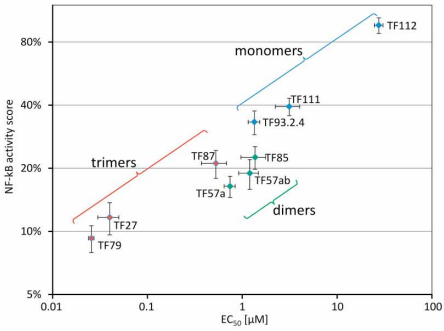


Figure 3. (A) Mass spectrometry-based proteomic approach. The identification of drug target proteins was achieved through the use of linker-coupled versions of artesunate compounds (immobilization on solid-phase beads). **(B) Direct correlation of anti-HCMV activity and NF-κB inhibition.** An NF-κB activity score was derived from data published in Hahn et al., 2018, Antiviral Res. by averaging the activity for each concentration. Resulting values were plotted against the EC50 values in double logarithmic.

■ **Cyclins and cyclin-dependent protein kinases (CDKs) serve as coregulators of cytomegalovirus replication.** An important focus of our investigations is the identification of central phosphorylation pathways of cellular protein kinases which are essential for the replication of herpesviruses. In this regard, the phosphorylation of viral regulator proteins by cellular protein kinases is particularly interesting. For the case of HCMV, the specific interaction between viral proteins and cellular protein kinases, especially cyclin-dependent protein kinases (CDKs), is presently investigated. The identification of regulatory consequences of such interactions will define novel aspects of virus-host cell interaction. Our recent data confirmed previous reports that CDK activity modulates the intracellular localization of the HCMV nuclear regulatory protein pUL69. CDK inhibitors induce a nuclear speckled aggregation of pUL69 in HCMV-infected fibroblasts. Moreover, experimental data proved a direct protein interaction between pUL69 and CDK9/cyclin T. Interestingly, we identified that the phosphorylation of pUL69 can be mediated through cellular CDK as well as viral pUL97 kinase activities. This finding supported the current postulate that pUL97 represents a viral CDK ortholog. Recently, we identified additional interactions between pUL97 and human cyclins of types T1, B1 and H (Figure 4). As a specifically important aspect, the demonstration of pUL97-cyclin complexes by biochemical settings (CoIP), mass spectrometry-based proteomics and bioinformatic modeling (Figure 5) addressed novel questions of the regulatory consequences cyclin-associated viral kinase pUL97. Our current concept suggests that the cyclins bound to pUL97 may recruit substrate proteins and may reinforce preferential events of pUL97-mediated substrate phosphorylation. Mutational analysis is presently performed and a CoIP-based interactomic analysis of pUL97 site-directed replacement and deletion mutants carrying putative defects in cyclin interaction refined our insight into the underlying regulatory details. Specific findings of the ongoing investigations are: (i) pUL97 interacts with cyclins B1 and H in a manner dependent on pUL97 kinase activity and phosphorylation or HCMV-specific cyclin modulation; (ii) pUL97-mediated *in vitro* phosphorylation of cyclins

is measurable for type B1 but not H, and no evidence is provided for mutual transphosphorylation between pUL97 and CDK7; and (iii) a cyclin T1/H-mediated bridging mechanism of pUL97 self-interaction is supported by current data. Future studies will have to define the differences in the molecular mode of interaction between pUL97 and at least three human cyclins.

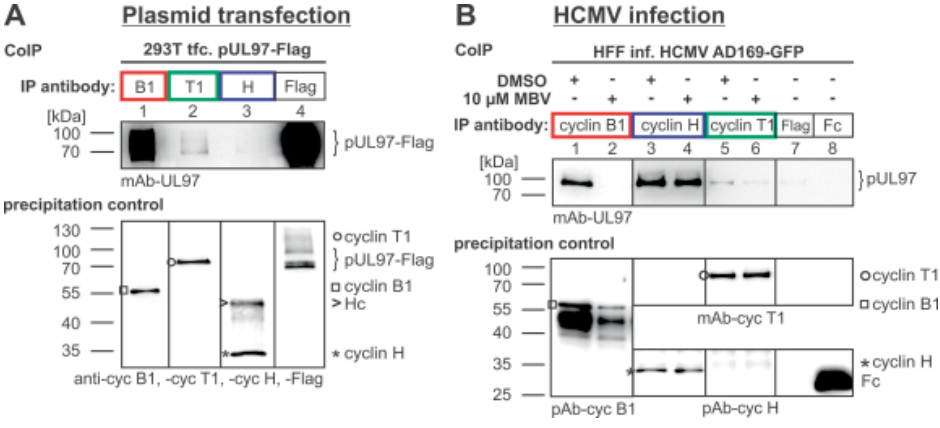


Figure 4. The interaction between pUL97 and cyclins B1, T1 and H depends on specific conditions provided by plasmid-transfected **(A)** or HCMV-infected cells **(B)**. Note, the strong interaction of cyclin B1 in both environments, which is strictly dependent on pUL97 activity, the relatively low signal of cyclin T1 interaction, which is independent of pUL97 activity, and the very strong cyclin H interaction, which is exclusively found within the environment of HCMV-infected cells.

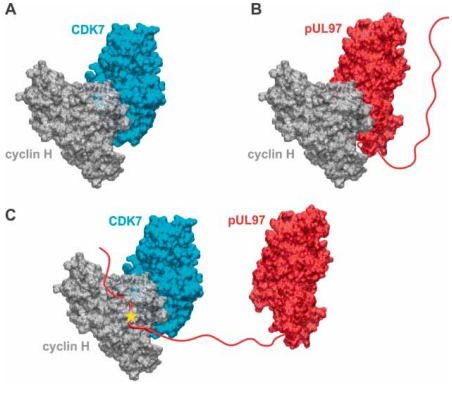


Figure 5. Structural model of the putative cyclin H-bridged interaction between pUL97 and CDK7. (A) Model of the binary CDK7-cyclin H complex. **(B)** Model of the binary pUL97-cyclin H complex. Both models were generated based on the homologous CDK9-cyclin T1 complex crystal structure using the strategy described before and show the canonical interaction via the large globular domain interfaces. The globular domain interfaces shown in **(A)** and **(B)** are overlapping and thus only one partner can interact with cyclin H via this interface. **(C)** Model of a putative ternary CDK7-cyclin H-pUL97 complex, in which the long unstructured N-terminal region of pUL97 is supposed to interact with cyclin H via an alternative binding motif or interface. A yellow star denotes a yet undefined modification of cyclin H induced by the HCMV-specific infectious environment that is required for pUL97 binding.

In addition to the viral CDK ortholog pUL97, also cellular CDKs have been characterized as coregulators of herpesviral replication by studies of our group and further investigators. Currently, we are performing a characterization of the interaction patterns and regulatory roles of individual CDKs (most of all CDK7) during HCMV infection of human fibroblasts and other cell types. Especially, CDKs and further protein kinases that possess importance for the replication of HCMV as well as other herpesviruses have been considered as potential antiviral drug candidates. In this regard, it appears promising that our current *in vitro* data prove the high antiviral efficacy of inhibitors of virus-relevant CDKs. In particular, two highly potent and selective inhibitors of CDK7 exert a broad and effective antiviral activity. These findings may be highly beneficial for the development of novel broad-spectrum antiherpesviral drugs.

- **Experimental development of antiherpesviral drug candidates based on protein kinase inhibitors.** Cytomegaloviral pUL97 is considered as a validated target enzyme for novel antiviral drugs. This seems particularly interesting due to the fact that pUL97 is already an essential part of conventional antiviral therapy, carrying out a pacemaker phosphorylation reaction on ganciclovir and related nucleoside analogs. For the development of a pUL97-directed antiviral strategy, we established quantification systems for pUL97 kinase activity and thereby identified novel chemical classes of compounds (quinazolines, indolocarbazoles, benzimidazoles and others) that inhibit the pUL97 kinase activity. Hereby, it was shown that these kinase inhibitors are able to block HCMV replication efficiently *in vitro* and *in vivo* and that the inhibitory effects on the levels of kinase activity and virus replication are linked. Our very recent study of quinazoline-type inhibitors of pUL97 indicated the high value of bioinformatic-based modeling approaches in the optimization of candidate compounds. An enlarged platform combining biochemistry-, bioinformatic-, structural biology- and medicinal chemistry-based approaches may substantially take forward our efforts of pUL97-directed drug design. In addition to the analysis of pUL97 inhibitors, a broad-spectrum antiherpesviral activity was identified shown for the CDK7 inhibitor LDC4297. This interesting compound, comprising an outstanding selectivity for CDK7, has been characterized by a kinome-wide evaluation (>330 kinases profiled *in vitro*). LDC4297 exerts an efficient inhibition of HCMV replication in primary human fibroblasts at nanomolar concentrations (EC50 24.5±1.3 nM) and exerts a broad antiherpesviral activity (whereas non-herpesviruses, i.e. adeno-, pox-, retro- and orthomyxoviruses, showed only intermediate or no sensitivity). Recently, we reported an *in vivo* analysis, using MCMV infection of $Rag^{-/-}$ immunodeficient mice, thus providing a proof-of-concept for the antiviral potency of LDC4297. Thus, the CDK7 inhibitor LDC4297 is a highly potent tool for the analyses of mutual interregulation between HCMV and CDK and represents a candidate compound for the study of broadly acting antiherpesviral compounds.

Collaborations

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Human Cytomegalovirus Gene Regulation

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■ **Introduction**. Human cytomegalovirus (HCMV) remains an important cause of mortality and morbidity in immuno-compromised patients such as transplant recipients on immunosuppressive therapy. Furthermore, HCMV is the most common cause of intrauterine infection which can lead to sensorineural hearing loss and mental retardation. Although progress in the diagnosis of HCMV infections has led to improved therapeutic strategies, treatment of HCMV induced disease suffers from the toxicity of the currently available antiviral drugs. In addition, in patients where longer therapy is necessary the emergence of drug-resistant viral strains is frequent. Therefore, the development of novel antiviral drugs is urgently required in order to improve the therapy of HCMV infections. Thus, one important aim of our laboratory is the characterization of molecular events that can be used as targets for new antiviral strategies.

■ **PML nuclear bodies: a cellular structure that mediates intrinsic immunity against viruses.** Microbial infections are not only controlled by innate and adaptive immune mechanisms but also by cellular restriction factors which give cells the capacity to resist pathogens. Unlike the innate and adaptive part of the immune system, that require pathogen-induced signaling cascades in order to be switched on, these so-called intrinsic immune mechanisms are mediated by cellular proteins that are constitutively expressed and active before a pathogen enters the cell, thus serving as a front-line defense. Our laboratory investigates whether a subnuclear structure, termed PML nuclear bodies (PML-NBs), contributes to the resistance of

cells against herpesvirus infections. PML-NBs are dot-like structures of the cell nucleus, that are defined by the distinct accumulation of specific cellular proteins like PML, hDaxx, Sp100 and ATRX (Figure 1). During the last ten years our laboratory could show, that these proteins act as cellular restriction factors by inducing a silencing of viral gene expression. Moreover, our research revealed that specific viral proteins (pp71 and IE1 of HCMV) are able to antagonize this cellular silencing mechanism (Figure 1). This establishes a delicate balance between cellular defense and viral antagonism which determines whether the herpesvirus enters the productive cycle or viral gene expression is silenced.

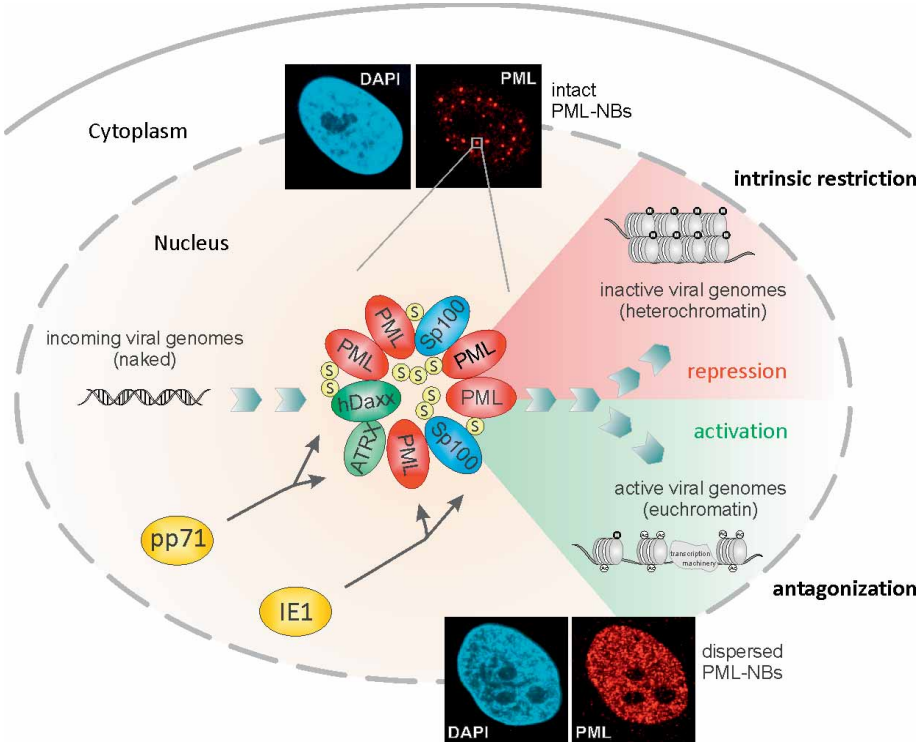

Figure 1: PML-NBs: a cellular structure that mediates intrinsic immunity against human cytomegalovirus. Viral effector proteins that are known to antagonize PML-NBs are shown in the left part of the figure.

■ **Molecular mechanism of PML-NB disruption.** During the last two years we could delineate the molecular mechanism how IE1 antagonizes PML-NBs. As evident from the crystal structure of IE1 that we solved in collaboration with Prof. Y. Muller and Prof. H. Sticht, this protein directly interacts with the PML coiled-coil domain via its globular core region and disrupts NB foci by inducing a loss of PML SUMOylation. We were able to demonstrate that IE1 acts via abrogating the *de novo* SUMOylation of PML. In order to overcome reversible SUMOylation dynamics, we made use of a cell-based assay that combines inducible IE1 expression with a SUMO mutant resistant to SUMO proteases. Interestingly, we

observed that IE1 expression did not affect preSUMOylated PML, however, it clearly prevented *de novo* SUMO conjugation. Consistent results were obtained by *in vitro* SUMOylation assays demonstrating that IE1 alone is sufficient for this effect. Furthermore, IE1 acts in a selective manner since K160 was identified as the main target lysine. This is strengthened by the fact that IE1 also prevents As_2O_3-mediated hyper-SUMOylation of K160 thereby blocking PML degradation. Since IE1 did not interfere with coiled-coil mediated PML dimerization we propose that IE1 either affects PML autoSUMOylation by directly abrogating PML E3 ligase function or by preventing the access to SUMO sites. Thus, our data suggest a novel mechanism how a viral protein counteracts a cellular restriction factor by selectively preventing the *de novo* SUMOylation at specific lysine residues without affecting global protein SUMOylation.

■ **SPOC1 acts as a novel cellular restriction factor against HCMV.** SPOC1 (survival time-associated PHD finger protein in ovarian cancer 1) functions as a regulator of chromatin structure and DNA damage response. It is able to bind H3K4me2/3 containing chromatin and promotes DNA condensation by recruiting H3K9 methyltransferases, such as SETDB1. SPOC1 was demonstrated to act as a restriction factor for Adenovirus (AdV) infection by repressing viral gene expression at the transcriptional level. To antagonize this repressive function, AdV targets SPOC1 for degradation immediately upon infection. Our results show that, in contrast to Ad-infected cells, SPOC1 is transiently upregulated during the early phase of HCMV infection. Furthermore, we demonstrate that SPOC1 overexpression severely impairs HCMV replication by repressing the initiation of viral immediate early (IE) gene expression. In accordance, a depletion of SPOC1 leads to an enhancement of IE gene expression. Since nuclear domain 10 (ND10) structures are crucial regulators of the onset of lytic infection, we investigated a possible inter-regulation of SPOC1 and ND10. Therefore, we compared the replication of wild-type HCMV and recombinant viruses lacking ND10 antagonistic proteins in primary human fibroblasts (HFF) with a stable SPOC1 knockout. While multistep growth curve analyses with wild-type HCMV strains displayed only a mild increase in replication efficiency, mutant viruses deprived of either immediate-early protein 1 (IE1) or pp71 replicated with clearly pronounced efficiency in the absence of endogenous SPOC1. We next analyzed the impact of SPOC1 depletion in combination with a knockdown of individual ND10 components on the onset of viral IE gene expression. Interestingly, the restrictive effect of SPOC1 was decreased in ND10 knockdown HFFs, indicating a cross-talk of different cellular factors in the intrinsic defense against HCMV. Since SPOC1 was shown to modulate the chromatin association of specific DNA compaction factors like KAP-1 and HP1-α, this inter-regulation suggests epigenetic synergy concerning the silencing mechanisms of SPOC1 and ND10.

■ **The autophagy initiating protein kinase Ulk1 exerts a proviral role during HCMV infection.** Research conducted during the last few years revealed that the cellular protein kinase Ulk1 exerts critical regulatory functions at the intersection of autophagy, innate immunity and inflammatory disorders. This protein was first described as autophagy-initiating protein kinase, however, recent evidence suggests that Ulk1 is an important component of different protein complexes involved in pathogen recognition. Furthermore, Ulk1 not only controls the onset of macroautophagy and mitophagy but also fine-tunes and negatively regulates inflammatory processes thus preventing immunopathology. We observed that Ulk1 is strongly upregulated after infection of primary human fibroblasts with human

cytomegalovirus (HCMV). In addition, we detected an enhanced phosphorylation of Ulk1 at various serine residues which are typically targeted by the cellular AMP-activated protein kinase (AMPK), a metabolic stress response kinase. Inhibition of AMPK activity reversed this HCMV-induced modulation of Ulk1 which correlated with an impairment of viral replication. Evidence for a proviral role of Ulk1 was also obtained by generating primary human fibroblasts with a stable Ulk1-knockdown which revealed a profound growth defect of HCMV in the absence of Ulk1. Furthermore, small molecule inhibition of Ulk1 kinase activity strongly interfered with HCMV replication. Collectively, these data suggest that Ulk1 may serve as a novel target molecule for antiviral therapy. Moreover, viral dysregulation of Ulk1 may contribute to immunopathology frequently observed in connection with HCMV infection.

■ **The UL69 of human cytomegalovirus: a regulator of viral mRNA export that is controlled by distinct post-translational modifications.** Human cytomegalovirus (HCMV) encodes the viral mRNA export factor pUL69, which facilitates the cytoplasmic accumulation of unspliced mRNA via interaction with the cellular RNA-helicases UAP56 or URH49. We reported before that pUL69 is posttranslationally phosphorylated by cellular CDKs and/or their viral orthologue pUL97. Here we set out to identify phosphorylation sites within pUL69 and characterize their *in vivo* importance for HCMV-replication. First, we performed MassSpec-based phosphosite mapping of pUL69 after immunopurification from AD169-infected HFF cells and identified several phosphorylation sites within the protein at 72hpi. However, in contrast to *in silico* analyses, which predicted numerous phosphosites within the functionally important N-terminus of pUL69, we failed to find any of those by our MassSpec analyses. We therefore compared the expression profiles of pUL69-mutants that carry individual or combinatorial substitutions of putative phosphosites within the pUL69 N-terminus by Phos-tag-SDS-PAGE, and provide evidence that S46, S49 as well as 2 of the serines 132, 133 or 134 were phosphorylated when pUL97 wildtype but not when its catalytically inactive derivative pUL97-K355M were coexpressed. Since pS46 and pS49 within alpha-helix 2 are both preceding a proline, we speculated that they might be substrate for Pin1-mediated peptidyl-prolyl *cis-trans*-isomerization and confirmed a complex formation of pUL69 and Pin1 by CoIP experiments. By performing NMR-experiments with (un)phosphorylated pUL69-peptides, we were able to exclude that phosphorylation affects the secondary structure of pUL69. However, our NMR-results strongly suggest that purified Pin1 catalyzes the *cis/trans*-isomerization of Proline 50 when S49 is phosphorylated. In accordance with our biochemical *in vitro* studies, multistep growth-curve analyses of recombinant HB15-derived viruses that carry S/T to A-substitutions within the pUL69 N-terminus revealed a severe growth defect. We therefore identified numerous phosphorylation sites within pUL69 and demonstrated that its N-terminal pUL97-phosphosite(s) are crucial for Pin1-mediated *cis/trans*-isomerization and efficient HCMV replication.

■ **Signaling of the HCMV-encoded G protein-coupled receptors pUS27**. Herpesviruses encode multiple G protein-coupled receptor homologues (vGPCRs) that have acquired unique properties to modulate cellular signaling. We identified a novel signaling capability of the vGPCR pUS27 of human cytomegalovirus (HCMV) that leads to strong NF-κB activation thus inducing the expression of chemoattractant cytokines. We demonstrate that the C-terminus of pUS27 directly interacts with TNF receptor-associated factor (TRAF) 6 resulting in canonical NF-κB activation. Intriguingly, signaling by pUS27 does not

depend on G protein-coupling and correlates with internalization to endosomes. Interestingly, disruption of a PDZ domain-binding motif at the C-terminus of pUS27 strongly enhances signaling indicating that the activity of this vGPCR is restrained by cellular PDZ proteins. A mass spectrometry-based analysis was performed to identify the factors that interact with the US27 C-terminus. Most prominent among the identified proteins were components of signaling complexes which are involved in the establishment of apico-basolateral polarity in epithelial cells. In order to further investigate the consequences of pUS27-dependent NF-κB activation, we performed a cDNA array to identify cellular genes regulated by US27. Using a 293 cell line with doxycycline-inducible expression of US27-FLAG we show that pUS27 strongly induces the mRNA levels of specific chemoattractant cytokines when it is uncoupled from negative regulation by PDZ proteins. Infection experiments of epithelial cells with US27 mutant cytomegaloviruses suggest that pUS27 also contributes to the upregulation of specific cytokines during viral infection. Since inflammatory bowel disease (IBD) is associated with a downregulation of polarity complex proteins this may unleash pUS27 signaling thus contributing to enhanced viral dissemination via the secretion of chemoattractant cytokines. In summary, our data reveal a unique and switchable TRAF6-dependent signaling activity of this vGPCR which may foster viral dissemination upon inflammation-mediated downregulation of constraining epithelial factors.

Collaborations

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Oncogenic Rhadinoviruses and Pathogen Discovery

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■ **Antiviral Immunotherapy against the human Cytomegalovirus.** We continue our longstanding cooperation with the group of Prof. Wolfgang Holter and PD Dr. Manfred Lehner, St.Anna Children's Hospital and Children's Cancer Research Institute, Vienna. Here we develop novel antiviral strategies using recombinant chimeric antigen - receptors (CAR) directed to CMV viral glycoprotein B or to cellular NKG2D. These transgenes are delivered by lentiviral vectors and as synthetic mRNA (Full et al., 2010); this research led us to the discovery that CMV infected cells are resistant to CAR-mediated T-cell killing in an HLA-recognition independent manner, with possible involvement of the CMV effectors UL36 and UL37x1, beyond their known anti-apoptotic functions (Proff et al., 2016, 2018). In a close cooperation with the biopharmaceutical company Amgen we investigate the feasibility of related BiTE®-based immunotherapies for CMV infection (Brey et al., 2018).

■ **Lymphocyte growth transformation by Herpesvirus saimiri (HVS)** is a useful tool for immunologist as well as a model that allows us to study episomal viral genomes. Our analysis of the viral episomal chromatin structure in human T-cells, together with a seminal characterization of episomal DNA replication (Alberter et al., 2011, Vogel et al., 2010), can serve to identify factors that regulate chromatin permissiveness within the vector genome and will allow sustained transgene expression from rhadinoviral vectors. CTCF is *the* chromatin organizer in eukaryotic cells and also important for the viral chromatin. CTCF protein binding to the HVS genome was studied in virus transformed human T lymphocytes (Zielke et al., 2012), revealing that a single CTCF binding site was crucial for the maintenance of viral episomes and the transformed state.

The viral effectors that HVS uses to transform human and monkey T-cells to antigen

independent growth are studied using virus-genetic approaches in the context of the viral genome, which we manipulate by standard molecular techniques and homologous recombination. These viral mutants are then studied in transformation assays *in vitro* with marmoset and human primary lymphocytes. We have shown that constitutive STAT3 activation by the Tip oncogene is not required for human T-cell transformation by HVS and that the Tip-Lck interaction is necessary for transformation and that IL2-dependence of transformation is coupled to a specific tyrosine residue – a finding that directed our research to the T-cellular IL2 signaling pathway and the role of STAT5.

■ Cellular restriction of the Kaposi sarcoma associated human herpesvirus 8 and related Rhadinoviruses.

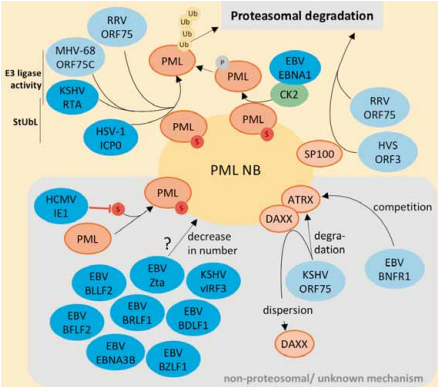

Figure 1. Herpesvirus proteins target the PML nuclear body (modified from Full et al., 2017).

KSHV/HHV8 is a human herpesvirus with close relationship to HVS, Rhesus Rhadinovirus (RRV) is the corresponding homolog from Old World Primates. We are investigating the potential of rhadinoviral proteins to disrupt PML nuclear bodies and other cellular functions, again employing recombinant viruses. This showed that gamma-herpesviral effectors antagonize nuclear domain 10 instituted intrinsic immunity in different ways. The HVS ORF3 was able to mediate the selective degradation of the cellular protein Sp100 (Full et al., 2012). The related ORF75 of KSHV was identified as an essential viral protein as it mediates disappearance of ATRX and dispersal of Daxx from ND10 (Full et al., 2014). Notably, the viral ORF75 protein RRV, despite more closely related to KSHV, resembles the HVS ORF3 in its predominant targeting of the major ND10 component SP100 in a proteasome dependent manner (Hahn et al., 2016). In a further search for antiviral restriction factors, Dr. Florian Full in cooperation with Prof. Michaela Gack (Chicago) demonstrated that the centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity (Full et al., 2018) and, in cooperation with the group of Prof. Jean-Laurent Casanova, we showed that human CIB1–EVER1–EVER2 complex governs keratinocyte-intrinsic immunity to β-papillomaviruses (de Jong et al., 2018).

■ Pathogen discovery and analysis using next generation sequencing.

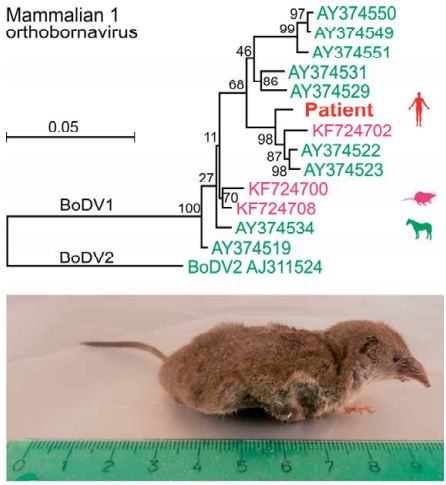

Figure 2. Phylogenetic tree demonstrating close relationship of BoDV-1 detected in a patient with encephalitis to sequences obtained from shrews and diseased horses.

Using next-generation sequencing (NGS), we attempt unbiased pathogen identification

from diagnostic samples of patients with presumed diseases of probable infectious origin. Here we recently detected Borna disease virus 1 (mammalian 1 orthobornavirus, BoDV-1) in brain tissue of a patient with fatal encephalitis of unknown origin (Korn et al., 2018), demonstrating that BoDV-1 is indeed pathogenic in humans. We further develop applications and use NGS in genome wide CRISPR/Cas9 knockout screens, in particular as a platform to search for cellular factors restricting the replication of Herpesviruses and other pathogens.

Collaborations

- Prof. Wolfgang Holter, PD Dr. Manfred Lehner, St.Anna Kinderspital and Children's Cancer Research Institute, Vienna, Austria
- Prof. Jae U. Jung, Molecular Microbiology & Immunology, University of Southern California, Los Angeles, USA
- Prof. Ronald C. Desrosiers, University of Miami Miller School of Medicine, Miami, USA, and Dr. Alexander S. Hahn, Deutsches Primatenzentrum, Göttingen

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- Interdisziplinäres Zentrum für Klinische Forschung, Teilprojekt A66 and J57 (to Dr. Full)
- H2020-MSCA-IF-2015, EC 703896 VGAP

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Oncoproteins of Primate Rhadinoviruses

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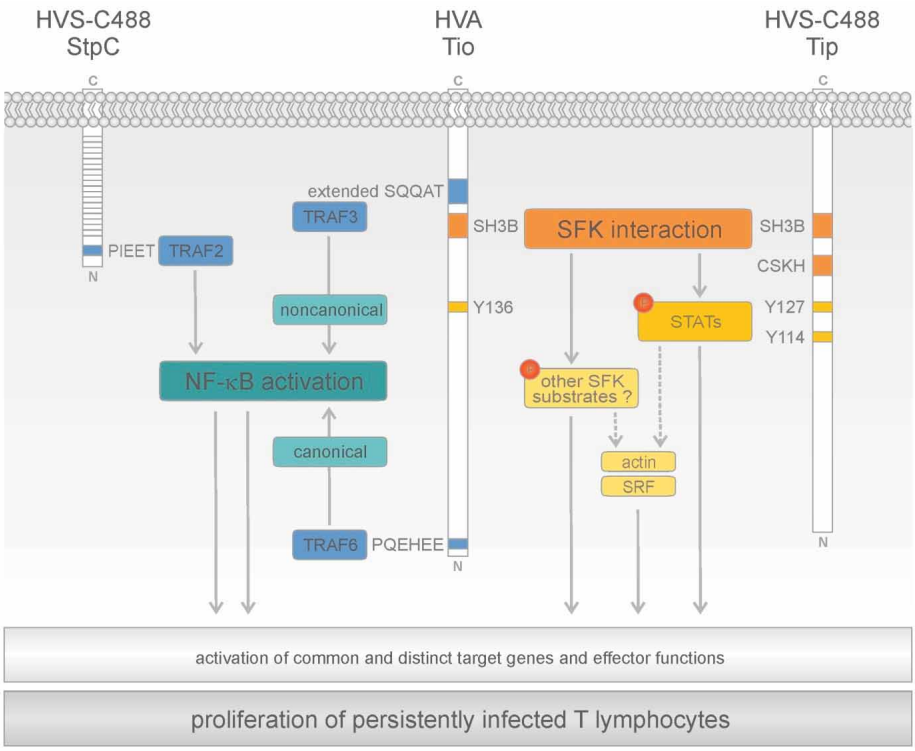
■ Proliferation, differentiation, and effector functions of T lymphocytes are regulated by an intricate network of multiple signaling pathways. They are triggered by ligation of the antigen-specific T-cell receptor (TCR), costimulatory receptors, cytokines, and chemokines. Dysregulated signaling is observed in diseases ranging from immunodeficiency to autoimmunity and T-lymphoid malignancies. We study T-lymphotropic rhadinoviruses, Herpesvirus saimiri (HVS) and Herpesvirus ateles (HVA), and their oncoproteins that support transformation of primary human T-cells to permanent growth in culture. Our analyses aim at the signaling pathways influenced by the viral oncoproteins to understand their role in regulation of T-cell proliferation and viral persistence.

The HVS oncoproteins StpC and Tip as well as the HVA oncoprotein Tio bind to Src-family kinases (SFK) and NF-κB-regulating TRAFs through distinct amino acid motifs. Accordingly, both SFK and NF-κB activity is required to maintain the growth-transformed phenotype of persistently infected T-cells.

■ **Interactions with Src-family kinases.** The Tyrosine kinase interacting protein (Tip) of HVS strain C488 was identified as a phosphoprotein associated with Lck, a major T-cell-specific SFK. Binding of Tip to Lck is based on modular interactions with the SH3, kinase, and SH2 domains. Similar to Tip, the Two-in-one (Tio) oncoprotein of HVA interacts with the SH3 and SH2 domains of several SFKs, including Lck and Lyn. Integrity of the SFK binding motifs in Tip and Tio is crucial for viral T-cell transformation. Specifically, targeting of SFK SH3 domains correlates with the viral capacity to transform human T lymphocytes.



Dependent on their SFK interaction sites, Tip and Tio induce the activation-specific phosphorylation of STAT1, STAT3, and STAT5. In addition, activation of STAT1 and STAT3 by Tip relies on tyrosine residue 114 (Y114), which may serve as an Lck substrate and, subsequently, as a STAT binding site. However, Tip mutant Y114F still supports viral T-cell transformation in culture. Likewise, activation of serum response factor (SRF) by Tip depends on SFK interaction as well as Y114. Thus, signaling intermediates, which are downstream of SFK SH3 binding and essential for viral transformation, remain to be identified.

■ **Interactions with TRAFs and NF-κB activation.** The Saimiri transformation-associated protein of subgroup C (StpC) harbors an N-terminal binding site for TNF receptor-associated factors (TRAFs), especially TRAF2, that is required for both canonical and noncanonical NF-κB activation. In contrast, Tio induces either of the two NF-κB pathways through a distinct molecular mechanism. Recruitment of TRAF6 to the N-terminal PQEHEE motif efficiently triggers canonical NF-κB activity. Inhibition of this pathway results in death of virus-transformed T lymphocytes. Recruitment of TRAF3 to a unique, extended TRAF binding motif is highly selective and induces noncanonical NF-κB activity without affecting the canonical pathway. Therefore, Tio represents a unique tool to study noncanonical NF-κB signaling in T-cells.

■ **Induction of MMP9 by Tio.** In an attempt to identify cellular genes induced by Tio in dependance of noncanonical NF-κB signaling, we identified MMP9 as a potential candidate. Ongoing analyses

indicate that Tio relies on the activity of canonical and noncanonical NF-κB as well as SFKs to upregulate this matrix metalloprotease involved in multiple biological processes including tumor cell invasion.

■ **Induction of IFN-γ.** Human lymphocytes transformed by H. saimiri subgroup C closely resemble mature, activated T-cells with a cytokine expression pattern skewed towards a Th1 phenotype. Accordingly, we identified the typical Th1 cytokine, interferon γ (IFN-γ), as a downstream target of the viral oncoproteins. While Tip-SFK interaction is essential for the basal induction, StpC augments IFN-γ expression through NF-κB activation. Recent experiments demonstrate that Tio also triggers IFN-γ production through SFK as well as canonical and noncanonical NF-κB activity. However, STAT1 phosphorylation depends on SFK interaction only and, thereby, excludes autocrine signaling. Thus, the role of IFN-γ in viral T-cell transformation in culture remains enigmatic. In infected animals, however, virus-induced IFN-γ production might contribute to viral pathogenesis.

Collaborations

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Human Herpesvirus 8 (Kaposi's Sarcoma-associated Herpesvirus)

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■ **KSHV/HHV-8.** Since the beginning of the AIDS epidemic, three human herpesviruses have been discovered. DNA fragments of human herpesvirus 8 (HHV-8), also termed Kaposi sarcoma-associated herpesvirus (KSHV) were first identified in 1994 in AIDS associated Kaposi's sarcoma biopsy specimens by representational difference analysis. DNA of this virus is invariably found in Kaposi's sarcoma, body cavity based lymphomas, and certain forms of Castleman's disease.

■ **Herpesvirus entry into host cells.** Entry of herpesviruses into host cells is seen as a multistep process involving several cellular receptors and at least four viral envelope glycoproteins of which only three (glycoproteins H, L and B) are conserved amongst all herpesviruses. The first step is attachment of the virion to the cytoplasma membrane. In most human herpesviruses, this step is mediated by one or more of the virus- or genus-specific glycoprotein(s) which bind to specific cellular receptor(s) and are often responsible for the cell tropism of the respective herpesvirus. In KSHV glycoprotein gpK8.1 is important for attachment of the virion to the cell by binding to heparansulfate. These strain-specific viral glycoproteins form complexes with the highly conserved glycoproteins H and L (gH/gL), either following receptor binding or already before, and seem to 'activate' gH/gL which – at least in some herpesviruses – is followed by endocytotic uptake of the virion. Interaction of activated gH/gL with glycoprotein B (gB) is then required to trigger the last step in herpesvirus entry: Fusion of the virion envelope with cellular membranes. This step is executed by trimeric gB which shares structural similarities with both class I and class II fusion proteins. As described above, a complex formed by the conserved glycoproteins gH/gL and at least one virus-specific receptor-binding protein is required to trigger gB mediated fusion in most herpesviruses.

■ **EphrinA2 receptor-tyrosinkinase (EphA2) and integrin αV are involved in KSHV entry.** Using immunoprecipitation and mass spectrometry we identified EphA2 as a cellular binding partner of KSHV gH/gL in 2012. We showed that EphA2 does not only bind to KSHV gH/gL with high affinity and specificity but that EphA2 is crucial for the infection of endothelial and epithelial cells by KSHV. Conflicting data have been published regarding the contribution of various integrins to KSHV entry. In order to further analyze the requirements for KSHV entry into target cells we constructed knock-out cell lines for EphA2, integrins αV and β1. Expression of EphA2 was reconstituted with several mutants in order to identify the contribution of intra- and extracellular domains to KSHV entry. Surprisingly, neither the intracellular domain nor the extracellular fibronectin domains of EphA2 were found to be required for KSHV infection of epithelial cells. However, presence of the juxtamembrane and tyrosin kinase domains enhanced infection about 2-fold (Figure 1).

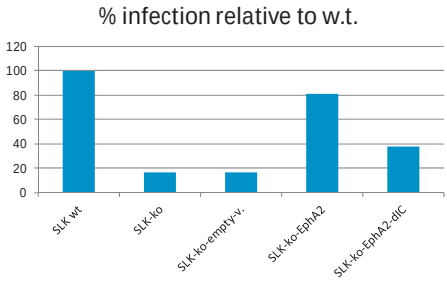

Figure 1: The intracellular part of EphA2 is not required to mediate KSHV infection. SLK wild-type cells (SLK w.t.), SLK cells with complete knock-out of EphA2 via CRISPR/Cas (SLK-ko), EphA2 k.o. cells transduced with either an empty vector (SLK-ko-empty-v), a vector expressing full-length EphA2 (SLK-ko-EphA2) or a vector expressing an EphA2 variant lacking the intracellular part of EphA2 (SLK-ko-EphA2-dIC) were infected with KSHV at a MOI of 0.5. Knock-out of EphA2 reduced the infection by approximately 85%. Reconstitution of the EphA2-expression in knock-out cells returned the infection rate to almost wild-type level.

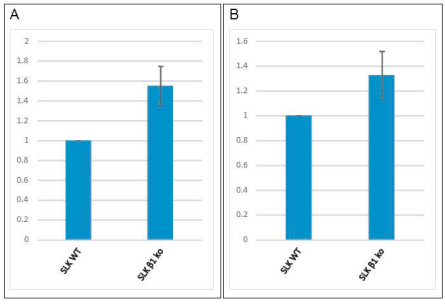

Figure 2: Knock-out of integrin β1 expression results in enhanced infection and increased integrin αV expression. A: SLK w.t and SLK β1 knock-out cells were infected with KSHV at a MOI of 0.5. **B:** relative expression level of integrin αV in SLK w.t. and SLK cells with knock-out of integrin β1.

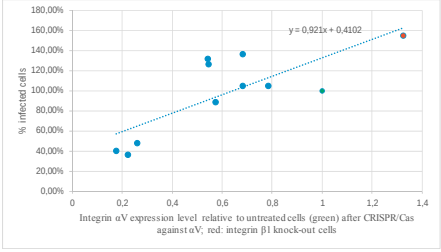

Figure 3: KSHV infection of SLK cells correlates with integrin αV expression. SLK cells were either left untreated (green) or transduced with a vector expressing a guide RNA targeted at integrin αV resulting in different levels of integrin αV expression (blue dots). The red dot represents SLK cells with a complete knock-down of integrin β1.

Several integrins including α3β1, α9β1 and αVβ3 have been published to mediate KSHV entry in both epithelial and endothelial cells. As we have been unable to reproduce blocking experiments using soluble integrins, we examined the effects of integrins on KSHV infection by using CRISPR/Cas knock-down or -out. Surprisingly, in contrast to published data the complete knock-out of integrin β1 did not reduce but rather enhance KSHV infection of SLK cells (Figure 2A). Interestingly, knock-out of integrin β1 enhanced expression of integrin αV (Figure 2B). We thus also examined the effect of integrin αV on KSHV infection by CRISPR/Cas mediated silencing. In contrast to integrin β1 we were not able to completely knock-out integrin αV. However, a marked reduction of αV expression levels could be reached. KSHV infection experiments revealed that reduction of integrin αV was associated with a dose-dependent reduction of KSHV infection (Figure 3).

■ **Antibodies against the extracellular domain of gH block KSHV infection.** We showed in the past that soluble EphA2 fused to the Fc-fragment of human IgG effectively blocks KSHV infection of epithelial and endothelial cells. This made it very likely that antibodies targeted at gH/gL will also effectively inhibit infection by KSHV. In collaboration with the groups of R. Eisenberg, G. Cohen and E. Berger we tested several polyclonal rabbit sera and murine monoclonal antibodies raised against recombinant gH/gL for inhibition of KSHV infection. Two out of four polyclonal rabbit antisera raised against gH/gL dose-

dependently reduced KSHV infection by up to 80% at a dilution of 1:10. Only one out of four monoclonal antibodies raised against gH significantly inhibited KSHV infection (Figure 4). Interestingly, this monoclonal antibody recognizes gH close to the transmembrane region.

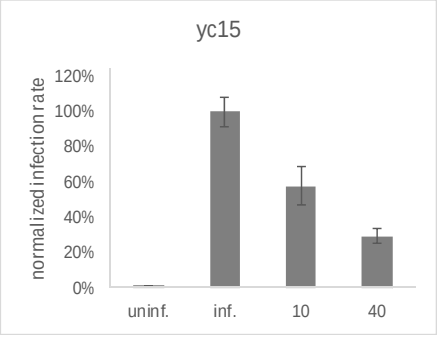

Figure 4: Infection inhibition by monoclonal antibody yc15 directed against gH. Abbreviations: uninf. = uninfected, inf. = infected without pre-incubation, 10/40 = respective antibody concentrations in µg/ml. SLK cells were infected with KSHV.219 pre-incubated with Mab yc15 for 45 min. Infection time was 30 min., afterwards cells were washed once with PBS-o to remove unbound virus. Two days after infection cells were harvested and the infection rate was determined by FACS. All measurements were normalized to the value of infection without pre-incubation. Samples were done in triplicates.

Collaborations

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Research on Epigenetics
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■ **The focus of the research group's interests** has been on the biological function of DNA methylation in genome stability and in the regulation of biological processes which are of interest in genetics (epigenetics) and medicine. In this report, we describe current results and plans for future projects.

■ Our concept

The human genome sequence contains about 28 million CpG pairs which are potential targets for the modification of cytidine- to 5-methyldeoxycytidine-residues (5-mC) by DNA methyltransferases. The distribution of 5-mC's across the human genome can vary with cell type. Depending on environmental conditions, CpG methylation patterns can be subject to change. Lacking a complete map of 5-mC locations in the human genome, how might one visualize these patterns which hold high functional significance for genomic stability and activity? Definite information is not available. The challenges raised by CpG methylation landscapes emerge from the large number of CpG's, and from the quest to decipher their functional meaning. By selecting the two following examples for more detailed inspection, we are fully aware that there will be many additional ones worth consideration.

(i) The presence of 5-mC residues in specific, functionally decisive positions of the genome is undoubtedly related to genetic activity.

(ii) Perhaps as importantly, the genome-inherent 5-mCpG versus CpG algorithms might be an important guardian of genomic stability, and capable of recognizing any threat against it. Much like innate and acquired immunity respond to the intrusion of foreign, often pathogenic molecules or cells, the CpG arrays are thought to be highly sensitive to the invasion of foreign

DNA into the cell. The CpG guardian might already be alerted by the contact of foreign nucleic acids with the cell surface or the mere application of techniques for gene transfer. This CpG alarm clock has probably developed early in evolution and, like other ancient biological defenses, has progressed and evolved over evolutionary times. This system is flexible and permits alterations, not always under strictly controlled conditions. Altered methylation patterns can be transmitted over cell generations, i.e. are at least in part inheritable.

The notion of a guardian for genome stability is caught between two contradicting, equally essential options. (i) Maintaining the inherited genome is the precondition for survival in the real world that abounds with a gamut of competing molecules and organisms. However, will defense of genome maintenance suffice as the major principle for survival? (ii) More realistically, the system requires the genetic and epigenetic potential to exploit competing organisms and their intruding foreign genetic information. Novel genetic and epigenetic information from foreign sources might be convenient to have around and could be constantly scanned for internal usefulness. Ubiquitous non-homologous recombination mechanisms enable the cell to incorporate newly-acquired foreign DNA into its own genome. Subsequently, this acquisition could be screened for internal advantage or might be eliminated from the cell's indigenous nucleotide sequence if advantageous. Selection in a competitive environment would then determine survival of propitious acquisitions of foreign DNA sequences.

We have set out to study changes in the cellular CpG methylation profiles upon introducing foreign DNA into mammalian cells. As stress factors served the genomic integration of foreign (viral or bacterial plasmid) DNA, virus infections or the immortalization of cells with Epstein Barr Virus (EBV). In several systems studied alterations in cellular CpG methylation and transcription profiles were observed to different degrees. In the case of adenovirus DNA integration in adenovirus type 12 (Ad12)-transformed hamster cells, the extensive changes in cellular CpG methylation persisted even after the loss of the transgenomic Ad12 DNA. Hence, stress-induced alterations in CpG methylation can be inherited independent of the continued presence of the transgenome. Upon adeno-virus infections, changes in cellular CpG methylation have not been observed. In EBV immortalized as compared to control cells, CpG hypermethylation in the far-upstream region of the human *FMR1* promoter decreased four-fold. In the wake of cellular stress due to foreign DNA entry, preexisting CpG methylation patterns were altered, possibly at specific CpG dinucleotides. Frequently, transcription patterns were also affected. As a caveat towards manipulations of cells with foreign DNA, such cells can no longer be considered identical to their unmanipulated counterparts.

- Doerfler, W., Weber, S., Naumann, A. (2018). Inheritable epigenetic response towards foreign DNA entry by mammalian host cells: a guardian of genomic stability, Epigenetics. 13: 1141-1153.
- Doerfler, W. (2019). Commentary – Epigenetic consequences of genome manipulations: caveats for human germline therapy and genetically modified organisms. Epigenomics. 11: 247-250.

■ Destabilization of the human epigenome: consequences of foreign DNA insertions

Aim: We previously reported changes of DNA methylation and transcription patterns in mammalian cells that carry integrated foreign DNA. Experiments were now designed to assess the epigenetic consequences after the insertion of a 5.6 kbp bacterial plasmid into the human genome.

Methods: Differential transcription and CpG methylation patterns were compared between plasmid-transgenomic and non-transgenomic cell clones by using gene chip microarray systems.

Results: In 4.7% of the 28,869 gene segments analyzed, the transcriptional activities were up-regulated (907 genes) or down-regulated (436 genes) in plasmid-transgenomic cell clones in comparison to non-transgenomic control clones. Frequent up-regulations were noted in small nucleolar RNA genes which affect RNA metabolism and in genes involved in signaling pathways (see Table 1).

Table 1 - Top canonical pathways for differentially expressed genes

- *EIF2* signaling
- Regulation of *eIF4* and *p70S6K* signaling
- Glutathione-mediated detoxification
- *FAK* signaling
- Insulin receptor signaling
- *ErbB4* signaling
- Small nucleolar RNA's

Genome-wide methylation profiling was performed for 361,983 CpG sites. In comparisons of methylation levels in five transgenomic versus four non-transgenomic cell clones, 3,791 CpG's were differentially methylated, 1,504 CpG's were hyper- and 2,287 were hypo-methylated (see Table 2).

Table 2 - Top canonical pathways for differentially methylated CpG's

- Neuropathic pain signaling in dorsal horn neurons
- Axonal guidance signaling
- *CREB* signaling in neurons
- Glutamate receptor signaling
- *GABA* receptor signaling
- Netrin signaling

Conclusions: The epigenetic consequences of foreign DNA integration can be considered a general effect also in human cells. We do not understand the role of transgenome size, CG content or copy number. The mechanism(s) underlying the observed epigenetic alterations are still unknown. Extent and location of alterations in genome activities and CpG methylation might depend on the site(s) of foreign DNA insertion. Genome manipulations in general – work with transgenomic or knocked cells and organisms – have assumed a major role in molecular biology and medicine. The consequences of cellular genome manipulations for epigenetic stability have so far received unwarrantedly limited attention. Before drawing far-reaching conclusions from work with cells or organisms with manipulated genomes, critical considerations for and careful analyses of their epigenomic stability could prove prudent.

■ Weber, S., Hofmann, A., Herms, S., Hoffmann, P., Doerfler, W. (2015). Destabilization of the human epigenome: consequences of foreign DNA insertions. Epigenomics. 7: 745-755.

■ Doerfler, W. (2016). Beware of manipulations on the genome: epigenetic destabilization through (foreign) DNA insertions. Invited Commentary – Epigenomics. 8: 587-591.

■ DNA methylation and transcription in HERV (K, W, E) and LINE-1.2 sequences remain unchanged upon foreign DNA insertions

Aim: DNA methylation and transcriptional profiles were determined in the regulatory sequences of the human endogenous retroviral (HERV-K, -W, -E) and LINE-1.2 elements and were compared between non-transgenomic and plasmid-transgenomic cells (see previous section for plasmid-transgenomic HCT116 cell clones).

Methods: DNA methylation profiles in parts of the HERV (K, W, and E) as well as LINE-1.2 sequences were determined by bisulfite genomic sequencing. The transcription of these genome segments was assessed by quantitative real-time PCR.

Results: In HERV-K, HERV-W and LINE-1.2 sequences the levels of DNA methylation ranged between 75 and 98%, while in HERV-E they were around 60%. Nevertheless, the HERV and LINE-1.2 sequences were actively transcribed. No differences were found in comparisons of HERV and LINE-1.2 CpG methylation and transcription patterns between non-transgenomic and the same plasmid-transgenomic HCT116 cell clones which showed altered transcription and CpG methylation profiles in other regions of their genomes (see previous section).

Conclusions: The insertion of a 5.6 kbp plasmid into the HCT116 genome had no effect on the HERV and LINE-1.2 methylation and transcription profiles, although other parts of the HCT116 genome had shown marked changes (Weber et al., 2015). Nevertheless, some of these heavily methylated repetitive sequences proved actively transcribed, probably because the large number of HERV and LINE-1.2 elements harbor copies with non- or hypo-methylated long terminal repeat sequences. These ancient genome constituents are possibly less sensitive to epigenetic alterations in the wake of foreign DNA insertions, since due to their long-term presence in the human genome, they might already have attained a “final” epigenetic mode.

■ Weber, S., Jung, S., Doerfler, W. (2016). DNA methylation and transcription in HERV (K, W, E) and LINE sequences remain unchanged upon foreign DNA insertions. Epigenomics. 8: 157-165.

■ Beware of manipulations on the genome: epigenetic destabilization through (foreign) DNA insertions

On the basis of the results summarized in Weber et al. 2015, and 2018, the notion has been pursued that manipulations of (mammalian) genomes in cultured cells can elicit genome-wide epigenetic alterations of transcriptional and methylation profiles and thus fundamentally alter the characteristics of the affected cells and organisms. It is unknown whether these events occur generally in all instances of foreign DNA insertions or whether manipulations other than insertions and excisions could have comparable sequelae. So far, we have not yet investigated the mechanisms which recognize and respond to insertions of foreign DNA into the cell nucleus or into the genome. Since the integration of foreign DNA stands at the center of many experimental approaches in biology and medicine, I consider our field of research of importance for the critical evaluation of results obtained from many lines of genome manipulations. The literature has practically kept silent on this issue. Several generally relevant implications of the consequences of foreign DNA insertion or of genome manipulations will have to be discussed in the following areas of biology and medicine: (i) Epigenetic factors in (viral) oncogenesis. (ii) Thoughts on epigenetics and evolution. (iii) Experimental approaches using genome manipulations.

■ Doerfler, W. (2016). Beware of manipulations on the genome: Epigenetic destabilization through (foreign) DNA insertions. Invited Commentary – Epigenomics. 8: 587-591.

Epigenetic Changes in Viral and Host Cellular DNA upon Virus Infections?

In our current work we have asked the question, whether the infection of mammalian cells with DNA viruses, like adenovirus type 12 (Ad12) or African Swine Fever Virus (ASFV) can lead to alterations in the CpG methylation status of (i) the intruding viral genome or (ii) the genomes of the recipient cells. The data available today are the following. (i) In the course of the productive infection of human HCT116 cells with Ad12 or of monkey cells with ASFV, the viral genomes do not become *de novo* methylated. For the Ad12 genome, it had been shown much earlier that the viral DNA inside virions is not CpG methylated. (ii) Preliminary findings suggest that there are no changes in the analyzed CpG's of human cellular DNA between 12 and 48 h after Ad12 infection. For ASFV-infected monkey cells, such investigations have not yet been done.

- Weber, S., Hakobyan, A., Zakaryan, H., Doerfler, W. (2018). Intracellular African Swine Fever Virus DNA remains unmethylated in infected Vero cells. Epigenomics. 10: 289-299.
- Weber, S., Conn, D., Herms, S., Hoffmann, P., Ramirez, C., Doerfler, W. Unpublished data.

Outlook on research in progress

The immortalization of human cells with EBV elicits changes in the cellular DNA methylation profile in a region far-upstream of the human *FMR1* gene promoter (Naumann et al., 2014). We have started to investigate this region as a potential indicator site in the human genome which is capable of responding to the entry of foreign DNA or of viruses with alterations in its methylation pattern. Should these earlier data be verified and expanded in more systematic studies, we intend to expose human cells in culture, e.g. cell line HCT116 and others, to various methods of gene transfer by transfection (Ca^{2+}-precipitation, lipofection, nucleofection), to the addition of foreign DNA to the culture medium of the cells, to the transfection with plasmid or viral DNAs, and to the infection with a wider selection of DNA or RNA viruses. In each set of experiments, the kinetics of possible changes in DNA methylation will be followed at various times after the application of the challenge. The far-upstream region of the *FMR1* promoter encompasses about 25 CpG dinucleotides and will be analyzed by the bisulfite sequencing technique which has been routinely used in our laboratory.

- Naumann, A., Kraus, C., Hoogeveen, A., Ramirez, C.M., Doerfler, W. (2014). Stable DNA methylation boundaries and expanded trinucleotide repeats: Role of DNA insertions. J Mol Biol. 426: 2554-2566.

Collaborations

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- Institute for Clinical and Molecular Virology, Erlangen University Medical School

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(iii) Contributions to Books

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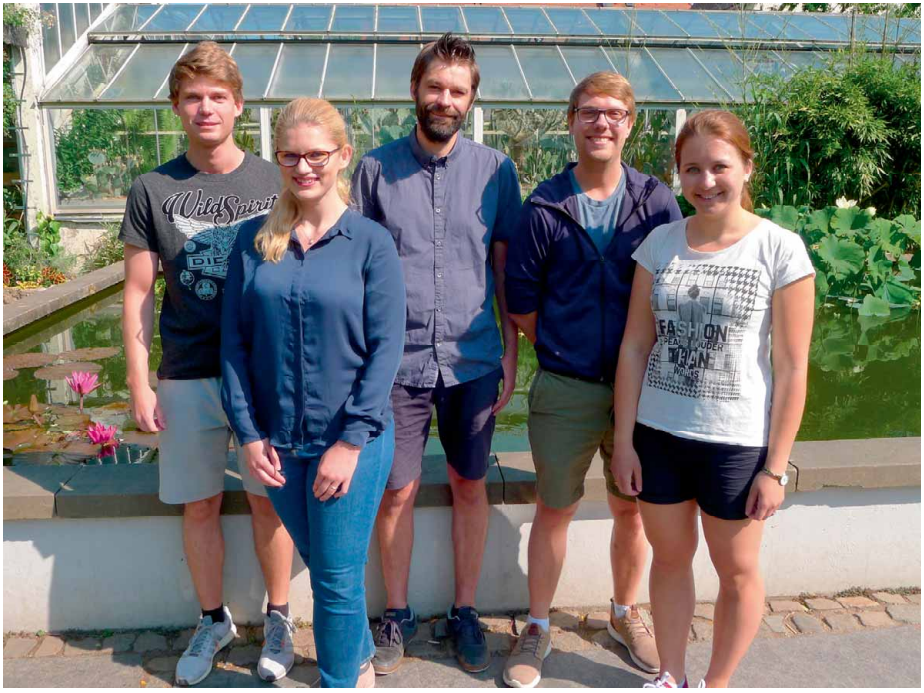
- Epigenetics of Infectious Diseases. W. Doerfler & J. Casadesús (Eds.). Springer Verlag: Cham, Heidelberg, New York, Dordrecht, London, 2017. doi: 10.1007/978-3-319-55021-3.

E. Forschungsschwerpunkt Antivirale Immunität
Research Focus Antiviral Immunity

Gene-based immunization strategies
Matthias Tenbusch



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■ Without any doubt vaccines are the most effective measures to prevent infectious diseases and promote individual and public health. Nevertheless, there are still a number of infectious disease where no or only inadequate vaccines are available. Therefore new vaccines and alternative vaccination platforms are still urgently needed. Currently, we address the potency of different gene-based vaccines in following projects:

■ **Mucosal immunity against viral respiratory tract infections induced by gene-based immunizations.** Influenza A Virus (IAV) and the Respiratory Syncytial Virus (RSV) are causative agents of severe respiratory tract infection especially in young children and elderly people. The

global disease burden is estimated to ~ 650 million cases per year for these two viruses leading to estimated 0.5 million deaths/year worldwide. While there is no prophylactic vaccine against RSV available at the time at all, there is an annual vaccination program against influenza viruses based mainly on tri- or quadrivalent inactivated influenza vaccines (T/QIV) which is recommended for certain risk groups (i.e. elderly or people with chronic lung diseases). Nevertheless, the overall vaccine efficacy is modest and the antibody mediated protection is rather short-lived and very strain-specific providing nearly no protection against drifted IAVs.

We developed in the last years DNA and adenoviral vector vaccines encoding the viral antigens hemagglutinin and nucleoprotein from IAV and the F protein from RSV. Furthermore, we evaluated a variety of application forms and determined the vaccine efficacy in the mouse and rhesus macaque model.

The most protective vaccination strategies included at least one immunization delivered via the mucosal route highlighting the exceptional role of local immune responses. We analyzed in detail the T-cell and antibody responses in the mucosal and in the systemic compartment.

Interestingly, a combination of a systemic DNA prime immunization with an intranasal adenoviral boost was the most effective schedule. This results in huge numbers of tissue-resident memory T-cells (T_{RM}) in the lungs which can very rapidly control infections with different heterologous IAV strains in the mouse model. Furthermore, this strategy also proved efficacy against an RSV infection in the rhesus macaque model.

In our recent work, we would like to decipher the correlates of protection for the different infection models and learn how the systemic and mucosal immune cells act together. Furthermore, we compare different viral vector systems and analyze possible synergistic effects in term of protection.

■ **Signal molecules of the innate immune system as genetic adjuvants.** From influenza infection models, it is known that not only the local antigen expression is important for the efficient induction of adaptive immune responses but also the induction of innate immune signaling.

Therefore, we used adenoviral vectors as genetic adjuvants which encode Interferons, components of the RIG-I/MAVS pathway or the effector molecules Interleukin-1ß and IL-18 derived from the inflammasome activation pathway.

So far, we could demonstrate that the co-delivery of an adenoviral vector encoding IL-1ß (rAd-IL-1β) dramatically improved the induction of the local immune response. Mucosal delivery of rAd-IL-1β enhanced HA-specific antibody responses including strain-specific neutralizing antibodies. Nevertheless, the beneficial effects on the local T-cell responses were much more impressive reflected by increased numbers of $CD103^+$ $CD69^+$ T_{RM}.

This increased immunogenicity translated into superior protection against infections with homologous and heterologous strains including H1N1, pH1N1, H3N2, and H7N7 (Figure 1). Inhibition of the egress of circulating T-cells out of the lymph nodes during the heterologous infection had no impact on the degree of protection underscoring the unique potential of T_{RM} for the local containment of mucosal infections.

The local co-expression of IL-1β and antigen lead to the activation of critical checkpoints in the formation of T_{RM} including activation of epithelial cells, expression of chemokines and adhesion molecules, recruitment of lung-derived $CD103^+$ DCs, and finally local T_{RM} imprinting.

Given the importance of T_{RM}-mediated protection at mucosal barriers, this study has major implications for the vaccine development against viral respiratory tract infections. Furthermore, it might be a step forward to the development of a broadly effective universal flu vaccine.

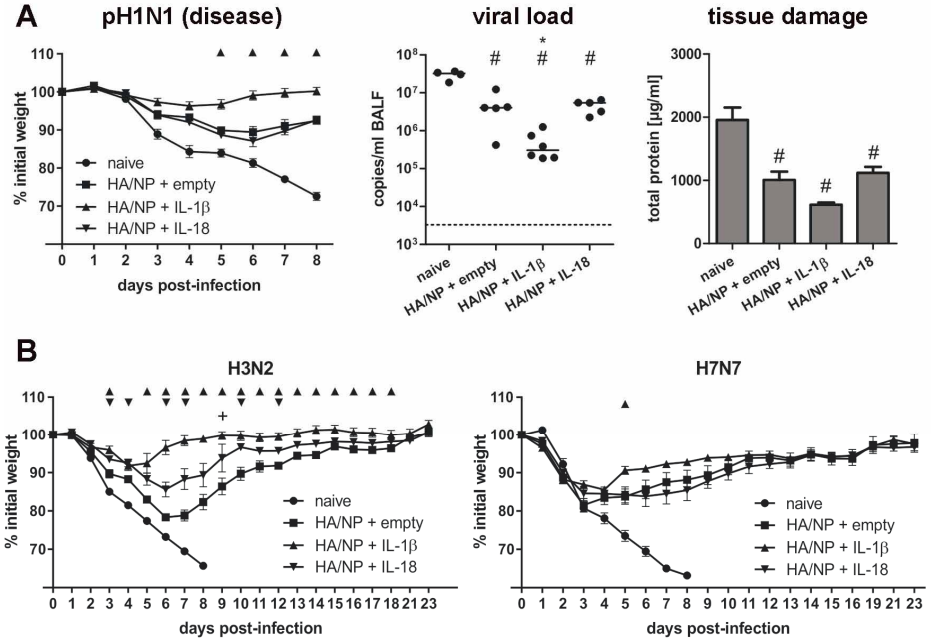

Figure 1: Enhanced heterosubtypic protection after co-delivery of rAd-IL-1β mediated by increased numbers of vaccine-induced T_{RM}. BALB/c mice were immunized with 2×10^8 particles of rAd-HA and rAd-NP plus 1×10^9 particles of either rAd-empty, rAd-IL-18, or rAd-IL-1β. Seven weeks after the immunization, mice were challenged with one of three heterologous influenza A strains, namely the pandemic pH1N1 (A), H3N2/HK68 (B, left) or H7N7/Sc35 (B, right). Weight loss is indicative for the disease progression. The viral loads in the lungs after the pH1N1 challenge were determined via qRT-PCR (A, middle) and the tissue damage were indirectly measured by the total protein content in the BALF (A, right).
#$p < 0.05$ vs. naive; * or the respective group sign, $p < 0.05$ vs. HA/NP + empty

■ **Evaluation of Ad19a as a novel vector for mucosal vaccination.** Replication-deficient adenoviral vectors have been extensively studied as vaccine vectors. The most common used systems are based on the adenovirus serotype 5. A possible drawback of this vector is the global seroprevalence of estimated 60-90% which might dampen the overall vaccine efficacy. Therefore, more rare human serotypes or adenoviruses from different species (e.g. simian adenoviruses) were evaluated as potential alternative vector systems. In this regard, we generated HA/NP-expressing Ad19a vectors and analyzed their immunogenicity and efficacy in the direct comparison to the Ad5-based vectors in our mouse model.

The adenoviral vectors were applied intranasally and induced detectable antigen-specific T-cell responses in the lung and in the spleen as well as robust antibody responses. A prior DNA immunization significantly improved the immunogenicity of both vectors and resulted in full protection against a lethal infection with a heterologous H3N2 virus. Nevertheless, the

Ad5-based vectors were slightly superior in reducing viral replication in the lung which corresponded to higher NP-specific T-cell responses measured in the lungs.

Taken together, we proved that the rare serotype Ad19a can be used as a vaccine vector in mucosal immunizations and, although slightly less immunogenic than Ad5, it is able to induce protective humoral and cellular responses. Thus, Ad19a expands the spectrum of available replication-defective vectors that are suitable for human vaccination.

■ **Therapeutic immunization in the allergen-induced asthma model.** In our group, we wanted to combine the advantages of gene-based vaccines with the efficient antigen presentation observed after Dendritic cell (DC) targeting. We generated single chain antibodies recognizing the DC-endocytic receptor DEC205, fused it to our antigen of interest and cloned the whole expression cassette in our adenoviral vector vaccines. Although we could demonstrate an enhanced antigen presentation, our studies revealed that we rather generate a local T-cell tolerance than antigen-specific effector T-cells probably due to missing maturation signals for the antigen-presenting DCs. A possible mechanism might be the induction of antigen-specific, regulatory cells instead of effector cells by immature DCs.

Based on these findings, we evaluated if the local induction of tolerance by this strategy might be suitable to dampen the allergen-specific immune response in a murine asthma model.

In this model, mice were sensitized with the model allergen ovalbumin resulting in a Th2 biased immune response which leads to airway hyper-responsiveness after inhalation of an OVA-containing aerosol. We treated this animal after the sensitization phase with adenoviral vectors encoding DC-targeted or non-targeted OVA and characterized the impact on the immunological and functional parameters of the asthma phenotype after challenge.

Indeed, only the intranasal application of vectors encoding the DC-targeted antigens was able to dampen the Th2 T-cell response and thereby reduce the strong eosinophilic infiltration and the airway hyper-responsiveness which are characteristics for the asthmatic phenotype.

This interesting approach should be further analyzed by using different vector systems and possibly new targeting strategies to improve the long-term effects of such a treatment. It might become an attractive alternative to the specific immune therapy which is until now the only causative treatment for allergies in patients.

Collaborations

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- Doktor Robert Pfleger Stiftung, „Signalmoleküle der angeborenen Immunantwort als genetische Adjuvantien bei adenoviralen Vektor-immunisierungen gegen das Respiratorische Synzytial Virus (RSV)"

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Protective Immune Response against Cytomegalovirus

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■ Human cytomegalovirus (HCMV) is an important, ubiquitously occurring, human pathogen in immunocompromised hosts.

The virus can cause severe disease in transplant recipients. In large parts of the world HCMV is also the most common viral infection acquired *in utero*. In the USA and Europe an estimated 0.2-1.2% of all live born infants are infected with HCMV and 5-15% of these babies develop long term sequelae resulting from congenital infection.

As a consequence of the importance of congenital HCMV infection for public health, the Institute of Medicine at the National Institutes of Health (NIH), USA, has ranked the development of a HCMV vaccine as a top priority.

A major obstacle for the development of a vaccine is a lack of knowledge of the nature and specificities of protective responses that should be induced by the vaccine. HCMV is a complex virus containing numerous antigens within the viral envelope that could be targets for protective antibodies. Glycoprotein B (gB) is an important target for neutralizing antibodies and hence an interesting molecule for intervention strategies such as vaccination or passive immunotherapy. We have used the murine model system of CMV (MCMV) to explore the potential of gB-specific monoclonal antibodies (mabs) in immunotherapy or prophylaxis. The mabs were found to bind to similar antigenic structures on MCMV gB that are represented in HCMV gB (see Figure 1). When these mabs were used in

immunodeficient RAG$^{-/-}$ mice to limit an ongoing infection we observed a reduction in viral load both with mabs having potent neutralizing capacity *in vitro* as well as mabs classified as non-neutralizing (Figure 2). In a therapeutic setting, nt mabs more potently reduced the viral burden compared to nnt mabs. Efficacy was correlated with sustained concentration of virus neutralizing mabs *in vivo* rather than their nt capacity *in vitro*. Combinations of nt mabs further augmented the antiviral effect and were as potent in protection as polyvalent serum from immune animals. Prophylactic administration of mabs before infection was also protective and both nt and nnt mabs equally prevented immune-deficient mice from the lethal course of infection. In summary, our data argue that therapeutic application of potently neutralizing mabs against gB represents a strategy to block CMV infection in immunodeficient hosts. When present before infection, both nt and nnt anti-gB mabs were equally protective.

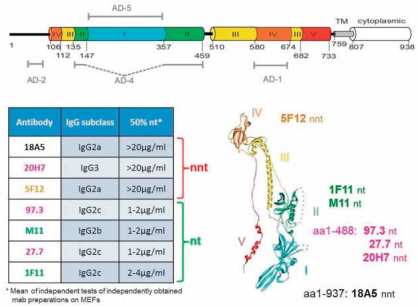


Figure 1. MCMV gB is targeted by monoclonal antibodies. (Top) Structural domains of MCMV gB displayed in different colors in analogy to the HCMV gB crystal structure. TM: transmembrane region. Numbers indicate the beginning of the domains. Antigenic regions (AD) corresponding to identified domains on HCMV gB are indicated. **(Bottom)** neutralizing (nt) and non-neutralizing (nnt) mabs belong to various IgG-subclasses (neutralization was assayed on MEF and concentrations of 50% neutralization of input virus are given in µg/ml). Mabs have target specificities comparable to the human situation as indicated in the 3D ribbon model of monomeric gB (bottom right).

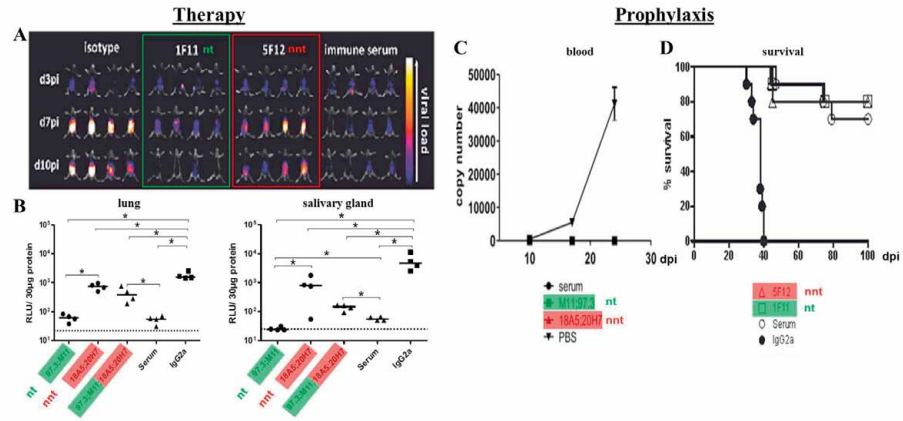


Figure 2. gB-specific antibodies protect from MCMV-infection. (A+B) Viral load of RAG$^{-/-}$ mice after therapy with nt or nnt antibodies or combinations of both. Mice were infected with 10^5 pfu MCMV157luc and treated with a total of 250 µg of the indicated IgG(s) or 200 µl serum per animal at three days after infection. **(A)** *In vivo* imaging was performed at the indicated days post infection (dpi). **(B)** Viral load in aliquots of organ homogenates containing 30 µg protein was determined 10 days after infection by a luciferase based assay. RLU: relative light units. Statistics: One way ANOVA using Bonferroni´s multiple comparison test *: $p<0.05$., dotted line: detection limit. **(C+D)** Protective capacity of anti-gB mabs following prophylactic application. A total of 250 µg IgG(s) per mouse or 200 µl serum/PBS was injected one day before infection with 10^4 pfu of MCMV157luc. **(C)** Blood was taken at the indicated dpi and MCMV load determined by qPCR. n = 4 in antibody treated groups and n = 3 in the PBS treated group. Values represent mean (SEM) of all mice within one group and duplicate determinations per sample. MCMV genome copy number is given per 1 µg total DNA. Detection limit: 1 copy/50 ng total DNA. **(D)** Survival was monitored for 100 days p.i. Statistics: log-rank (Mantel-Cox) test: $p < 0.0001$. Representative data from 2 independent experiments.

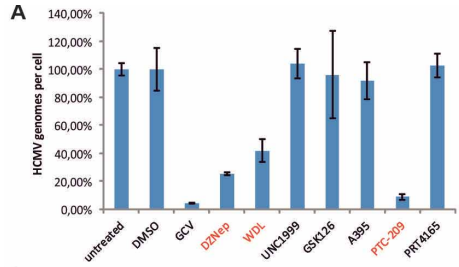
Dr. Nina Reuter (IZKF, subproject J45) – Modulation of PRC2 by HCMV IE2

Chromatin-based modifications of herpesviral genomes crucially dictate the outcome of infection. Host cell multiprotein complexes like PML bodies or the Polycomb repressive complex 2 (PRC2) have been identified as regulators of viral gene expression on the epigenetic level. We investigated the role of PRC2 and its related complex PRC1 for HCMV infection and analyzed the mechanisms HCMV has evolved to modulate PRC1/2 function for its own benefit.

■ **Role of PRC1/2 during lytic HCMV replication.** To address the relevance of PRC1/2 activity for the productive life cycle of HCMV, we dissected the levels of PRC1/2 core components following HCMV infection. This revealed that all major PRC1 and 2 factors are massively upregulated upon infection and recruited into viral replication compartments (VRCs; sites of viral DNA amplification) as infection progresses. Interestingly, however, the repressive histone marks instituted by PRC1/2 turned out to be specifically excluded from these sites suggesting a role of both complexes in viral DNA synthesis independent of their repressor activity. Indeed, using primary human foreskin fibroblast (HFF) knockdown cells in which individual PRC1/2 core factors were depleted by expression of respective shRNAs, we could show that PcG proteins are required for an efficient HCMV genome amplification. This is in accordance with recent reports from literature that identified a novel role of PcG factors in regulating the normal progression of cellular DNA replication.

Since PRC1/2 have emerged as promising drug targets in cancer therapy, we were able to test a series of diverse PRC1/2 inhibitory substances (Figure 3, A and B). All of these agents inhibit the enzymatic activity of the targeted repressor complex. Importantly, some substances additionally induce a destabilization of the respective complex, which is known to go along with a downregulation of certain PRC core components. Intriguingly, only substances which negatively affected complex stability like DZNep, Wedelolactone (WDL) or PTC-209 were able to compromise HCMV genome synthesis, while inhibition of PRC1/2's enzymatic activity alone (UNC1999, GSK126, A395 and PRT4165) had no effect. Taken together, this leads to the overall assumption that regulation of DNA amplification by PRC1/2, which is poorly defined yet, occurs in an enzymatic-independent manner (non-canonical mode of action).

■ **Regulation of PRC1/2 activity by the HCMV effector protein IE2p86 (IE2).** In former studies, we discovered an interaction between the HCMV transactivator protein IE2 and the PcG protein EED, which is a shared component of both complexes, PRC1 and 2. This suggests that HCMV has the capacity to regulate PRC1/2 activity for its own benefit (Figure 3C). To test this theory, we generated recombinant viruses lacking the EED interaction interface within IE2. Multi-step growth curve analysis revealed a severe growth defect of the EED interaction-deficient IE2 mutants in comparison to wildtype (wt) HCMV. In accordance with our hypothesis, we observed an impaired intracellular accumulation of newly synthesized viral DNA in case of the mutant viruses which resulted from an incomplete relocalization of PcG proteins into VRCs when compared to wt HCMV. In summary, we identified a novel interaction between IE2 and EED, which contributes to the recruitment of PcG proteins into VRCs for efficient HCMV DNA replication.



B

Substance	Target	Inhibition of		
		Enzymatic activity	Complex stability	HCMV DNA replication
DZNep	PRC2	+	+	+
WDL	PRC2	+	+	+
UNC1999	PRC2	+	-	-
GSK126	PRC2	+	-	-
A395	PRC2	+	-	-
PTC-209	PRC1	+	+	+
PRT4165	PRC1	+	-	-

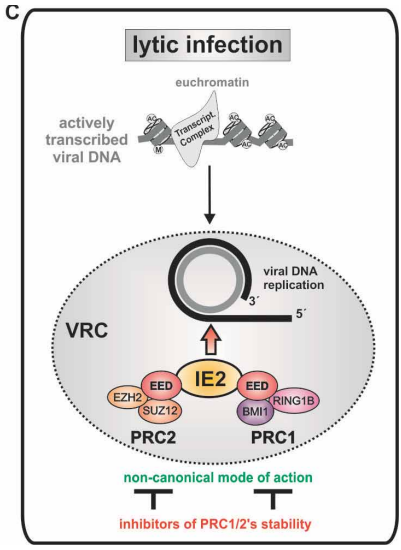


Figure 3. Role of PRC1/2 for lytic HCMV infection. (A) Quantification of viral genome copies following treatment of infected HFFs with the indicated PRC-inhibitors or Ganciclovir (GCV). **(B)** List of PRC1/2 inhibitors, their characteristics and effect on HCMV DNA replication. **(C)** Scheme: PRC1/2 are recruited by the HCMV IE2 protein into VRCs for efficient genome amplification. Both PRCs function in a non-canonical manner as they can only be inhibited by compounds that target complex stability.

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HIV Vaccine Research
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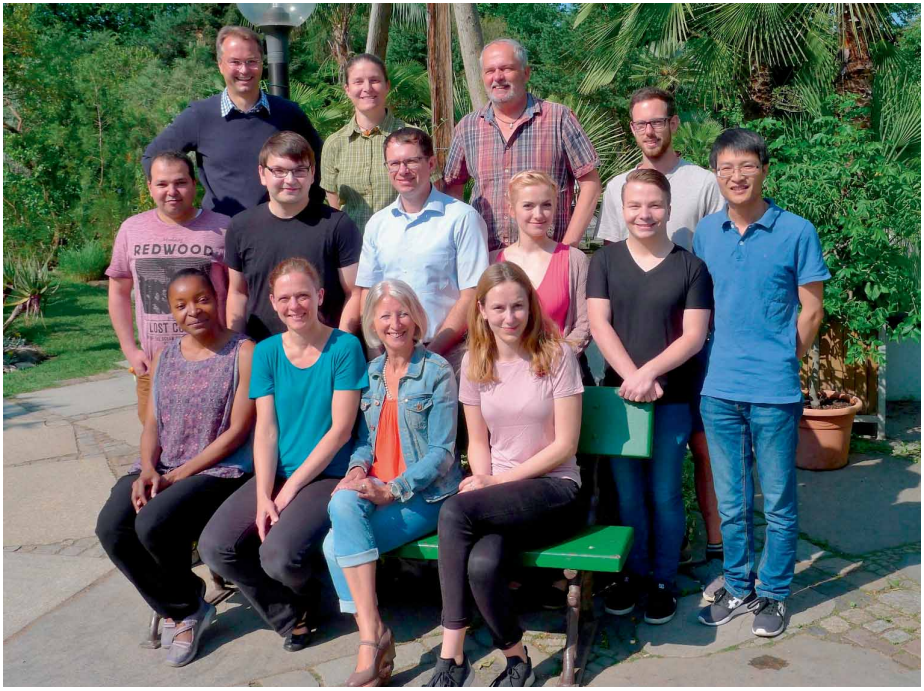

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■ With annual HIV infection rates still exceeding two million people a year, development of an HIV vaccine remains a world-wide urgency. The HIV vaccine research group is therefore exploring novel vaccination strategies and aims at a better understanding of immune responses that are induced by HIV or are required for protection. Currently, the following projects are pursued:

PI Überla

■ **Improving antibody responses to particulate vaccines by intra-structural help.** Antigen-specific T helper cells provide critical signals for cognate B-cells to differentiate into memory B-cells and plasma cells. In the context of particulate vaccines composed of different proteins, T helper cell epitopes and B-cell epitopes do not need be covalently linked. HIV-Env specific B-cells for example can internalize virus-like particles (VLPs) containing HIV Env and Gag. This leads to presentation of Env- and Gag-derived peptides on their MHC-II molecules explaining our observation that Gag-specific T helper cells can provide help for Env-specific antibody responses. In mouse experiments, Gag-specific T helper cells not only enhanced anti-Env IgG levels up to 100-fold but also modulated the IgG subtype response. A major aim of our research is therefore to develop novel vaccine platforms that exploit T helper cells induced by common licensed vaccines to improve the antibody response to heterologous viral antigens.

As a proof-of-concept, we introduced T helper cell epitopes of tetanus toxoid (TT) into HIV VLPs and immunized naïve mice or mice that had been immunized by Tetanol, a commercially available Tetanus vaccine, with HIV VLPs. Much higher HIV Env IgG1 antibody responses were observed in Tetanol-immunized mice that received VLPs containing the TT T helper cell epitopes than in naïve mice receiving the same TT-VLPs or Tetanol-primed mice receiving VLPs lacking the TT epitopes. Since the IgG1 subtype response induced in Tetanol-primed mice has less efficient Fc-effector functions we also identified T helper cell epitopes induced by HBVAXPRO, a licensed hepatitis B vaccine, and incorporated them into HIV VLPs. We currently exploring intrastructural help effects induced by different hepatitis B vaccines. To prepare for clinical studies, we have also identified HB-virus S-antigen-specific T helper cell epitopes recognized by most human vaccines.

In addition to VLP vaccines, liposomes may also be an attractive vaccine platform to harness T helper cells induced by licensed vaccine. In collaboration with Polymun Scientific Immunbiologische Forschung GmbH the incorporation of T helper cell epitopes into liposomes was optimized and we are currently exploring the coupling of HIV Env trimers to the surface of liposomes.

■ **Avoiding HIV-specific T helper cells to improve vaccine efficacy.** This project follows the innovative strategy to improve the efficacy of HIV vaccines by induction of affinity-matured HIV Env antibodies in the absence of HIV-specific T helper cells. The rational behind this strategy is based on observations that passive immunization with neutralizing antibodies can prevent infection and evidence that HIV-specific cellular immune responses may increase the susceptibility of acquisition of HIV infection. Since induction of the neutralizing antibodies is expected to depend on T-cell help, the project explores in relevant animal models the possibility to substitute HIV-specific T-cell help by T helper cells with other specificities.

■ **Sterilizing immunity after passive immunization.** Antibodies targeting the HIV-1 Env protein have been shown to prevent systemic infection in non-human primate models of AIDS. To explore whether these antibodies can block infection of the “first cell” at the viral portal of entry,

challenge viruses based on simian immunodeficiency virus (SIV) were developed that use HIV-1 Env for entry into target cells during the first replication cycle, but then switch to SIV Env for all subsequent rounds of infection. Passive immunization of monkeys with a broadly neutralizing antibody binding to Env of HIV-1, but not SIV, prior to rectal exposure to the switching challenge virus led to a >50-fold reduction of HIV-1 Env-mediated infection events. Inhibition of infection was also detected under non-neutralizing conditions. Based on the Env switching challenge virus a simultaneous challenge model is currently developed to address the breadth of protection in a non-human primate model.

PI Temchura

■ **Direct effects of HIV-1 derived lentiviral particles on activation and differentiation of naïve cognate B-cells.** Since little was known about the direct impact of VLPs on antigen-specific B-cells, we incorporated hen egg lysozyme (HEL) into VLPs derived from HIV (HEL-VLPs) to study their effect on HEL-specific, B-cell receptor (BCR) transgenic B-cells. We observed that B-cells preferentially bind and internalized cognate VLPs *in vitro*. HEL-VLPs were able to effectively cross-link BCRs, increase expression of activation and co-stimulatory molecules, and enhance proliferative responses. Additionally, the B-cell phenotype was shifted toward a germinal center pattern with further differentiation into memory and IgG3- and IgA-producing cells. Upon activation by HEL-VLPs, some cognate B-cells were able to produce CD40L, which might provide the required co-stimulatory signals in the absence of $CD4^+$ T-cells *in vitro*. The patterns of cognate B-cell activation obtained open up the path for the development of VLP-based vaccines inducing rapid humoral responses in patients with AIDS or after organ transplantation when $CD4^+$ T-cell function is impaired.

In vivo, we compared the efficacy of HEL-VLPs, delivered by subcutaneous (*s.c.*) or intravenous (*i.v.*) immunization to simultaneously stimulate primary cognate B-cell proliferative responses in different lymphoid organs. The observed differences argue for further studies on the quality of immune responses after intravenous administration of VLPs, an approach rarely pursued in the past.

■ **Generation of T follicular helper like cells *in vitro*.** T follicular helper (TFH) cells provide help for B-cells and are important for the formation and maintenance of germinal centers. Using co-cultivation of TCR-transgenic $CD4^+$ T-cells together with dendritic and BCR-transgenic B-cells in the presence of cognate VLPs, we induced co-expression of the TFH-master regulator transcription factor BCL-6 together with CXCR5 in up to 40% of the $CD4^+$ T-cells. Other phenotypic markers of for TFH cells could additionally be detected in these cells. Production of IL-21 and isotype switching by B-cells to IgG1 in the presence of induced TFH-like cells indicate a helper function of these cells *in vitro*. Thus, our study presents a robust experimental system for efficient generation of TFH-like cells *in vitro* and confirms the importance of cognate B- and T-cell cross-talk for the TFH-differentiation process.

■ **Testing of calcium phosphate nanoparticle-based vaccines.** Different kinds of synthetic nanoparticles have been suggested for vaccination. However, there are some advantages to use calcium phosphate nanoparticles (CaP-NPs) for targeted delivery of antigens: CaP is a mineral component of mammalian bone and therefore not harmful to the body, CaP-NPs can be prepared in a multi-shell way in order to protect biomolecules inside and after cellular uptake release their cargo inside the cell upon lysosomal dissolution at lower pH. Their surfaces can be covalently functionalized with biomolecules to an effective cell targeting. In this collaborative project with Prof. Epple (Essen), we

performed a side-by-side comparison of CaP-NPs functionalized with HEL protein (CaP-HEL-NPs) on targeting, binding and internalization by cognate B-cells *in vitro*. CaP-HEL-NPs were preferentially bound and internalized by HEL-specific B-cells. They effectively cross-linked B-cell receptors and were 100-fold more efficient in the activation of B-cells than soluble HEL. *In vivo,* we explored different administration routes for the CaP-HEL-NPs and confirmed their ability to reach draining lymph nodes and deliver the protein in its native conformation to the B-cell areas. By using well-defined immunological adjuvants we increased the immunogenicity of CaP-HEL-NPs and were able to modulate the strength and quality of the systemic and the mucosal humoral immune responses. The results indicate that CaP-NPs represent a flexible platform to modulate humoral immune responses on demand that can be adapted to the particular needs of vaccines targeting various diseases.

PI Nganou

- **Studying the quality and sustainability of vaccine-induced T-cell responses in ART-treated HIV infection.** HIV infection causes profound and often irreversible changes to the innate and adaptive immune system. For example, a permanent state of immune activation as well as depletion and dysfunction of $CD4^+$ T-cells that are important regulators of humoral and cellular responses, all contribute to an overall impaired immunity even in ART-treated HIV infection. The main aim of this project is to study the effect of ART-treated HIV infection on the immunity gained from vaccines administered prior to HIV infection. For this purpose, an initial focus is set on immune responses of adults to the measles virus and tetanus toxin (both primed in childhood). The various objectives currently being evaluated include measurements of (i) cellular and soluble markers of inflammation, (ii) antigen-specific T-cell responses, (iii) antigen-specific antibody levels and (iv) transcriptome analysis of sorted antigen-specific T-cells. Gaining a deeper understanding of how HIV infection alters antigen-specific responses may provide clues for how these responses could be improved to the benefit of an enhanced vaccine-induced protective immunity. Samples from HIV-infected subjects are obtained in collaboration with Prof. Dr. med. Thomas Harrer (Medizinische Klinik 3 – UK Erlangen).

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- Prof. Rich Wyatt, The Scripps Research Institute, La Jolla, USA
- Prof. Dr. Huimin Yan, Institute of Virology, Wuhan, China

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- EU, European AIDS vaccine initiative 2020 (EAVI 2020)
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Reviews and Book Chapters

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F. Aktivitäten in Klinischer Diagnostik
Activities in Clinical Diagnostics

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- Misir, Hülya
- Murrmann, Susanne

Untersuchungsspektrum/Spectrum of Laboratory Tests

- **Neutralisationstest** zum Nachweis von Antikörpern gegen
  Neutralization assay for the detection of antibodies against
  Coxsackieviren B1-B6
  Poliovirus Typ 1 und 3

- **Indirekte Immunfluoreszenz** zum Antikörpernachweis
  Indirect immunofluorescence for antibody detection
  Epstein-Barr-Virus-Capsid-Antigen IgA-Antikörper
  Humanes Herpesvirus Typ 6 (IgG-Antikörper, IgM-Antikörper)
  Humanes Herpesvirus Typ 7 (IgG-Antikörper, IgM-Antikörper)
  Humanes Herpesvirus Typ 8 (IgG-Antikörper)

- **Antigennachweise** mit monoklonalen Antikörpern in der Immunfluoreszenztechnik aus Zellkulturmaterial
  Antigen detection *via* immunofluorescence with monoclonal antibodies from cell culture material
  Herpes-simplex-Virus (einschl. Typendifferenzierung)
  Adenoviren
  Enteroviren (gruppenspezifisch)
  Coxsackie-Viren A9, A24, B1-B6
  Echoviren 4, 6, 9, 11, 30
  Enterovirus 70 und 71
  Poliovirus 1-3
  Masernvirus
  Mumpsvirus
  Rubellavirus
  Varizella-Zoster-Virus

- **ELISA- (ELFA-, CLIA-, CMIA-)Tests** für den Antikörpernachweis gegen:
  ELISA (ELFA, CLIA, CMIA) tests for the detection of antibodies against:
  Adenoviren (IgG- und IgA-Antikörper)
  Cytomegalovirus (IgG- und IgM-Antikörper, IgG-Aviditätstestung)
  Epstein-Barr-Virus (anti-VCA-IgG, anti-VCA-IgM, anti-EBNA-IgG)
  Herpes-simplex-Virus (IgG- und IgM-Antikörper)
  Varizella-Zoster-Virus (IgG- und IgM-Antikörper)
  Parvovirus B19 (IgG- und IgM-Antikörper)
  HIV-1 und HIV-2
  HTLV-I/II (menschliche T-Zell-Leukämie-Viren)
  Enteroviren (IgG- und IgM-Antikörper)
  FSME-Virus (IgG- und IgM-Antikörper)
  Mumpsvirus (IgG- und IgM-Antikörper)
  Masernvirus (IgG- und IgM-Antikörper)
  Rubellavirus (IgG- und IgM-Antikörper)

- **Immunchromatografische Schnelltests**
  Rapid immunochromatographic tests for the detection of antibodies/antigens
  für den Antikörpernachweis gegen Dengue-Virus Typ 1-4 (IgG- und IgM-Antikörper)
  zum Nachweis von Denguevirus-NS1-Antigen
  zum Nachweis (Bestätigung und Differenzierung) von Antikörpern gegen HIV-1 und HIV-2

- **ELISA-/CLIA-/CMIA-Tests** in der **Hepatitis-Serologie** für folgende Parameter:
  ELISA/CLIA/CMIA tests in **hepatitis serology**
  Hepatitis-A-Virus-Antikörper
  Hepatitis-A-IgM-Antikörper
  HBs-Antigen
  HBs-Antigen (quantitativ)
  HBe-Antigen
  HBs-Antikörper
  HBc-Antikörper
  HBc-IgM-Antikörper
  HBe-Antikörper
  Hepatitis-C-Virus-Antikörper
  Hepatitis-Delta-Antikörper

- **Immunoblot-Tests** zum Antikörpernachweis für folgende Viren:
  Immunoblot assays for antibody detection against the following viruses:
  Bunya-/Hantaviren (IgG, IgM für Hantaan-Virus, Puumala-Virus, Dobrava-Virus, Seoul-Viren und Sandfliegenfieber-Virus Toscana)
  Hepatitis-C-Virus
  Hepatitis-E-Virus (IgG- und IgM-Antikörper)
  Herpes simplex-Virus Typ 1 und 2 (typspezifische Antikörper)
  HTLV-1 (menschliches T-Zell-Leukämie-Virus Typ 1) und HTLV-2
  Parvovirus B19 (IgG- und IgM-Antikörper)
  Tropische Fieber-Viren (IgG und IgM für Chikungunya-, Dengue- und Zikavirus)

- **Standard-Zellkulturen** für die Anzüchtung von Viren
  Standard cell cultures for virus isolation
  HeLa-Zellen
  Vero-Zellen
  RD-Zellen
  Hep2-Zellen
  Humane Vorhautfibroblasten

- **Nachweis viraler Nukleinsäure** mittels **PCR** oder anderen Nukleinsäure-Amplifikationsmethoden für folgende Erreger:
  Detection of viral nucleic acids using **PCR** or other nucleic acid amplification methods
  Herpes simplex-Viren Typ 1 und 2
  Varizella-Zoster-Virus
  Cytomegalovirus
  Epstein-Barr-Virus
  Humanes Herpesvirus Typ 6 und 7
  Humanes Herpesvirus Typ 8 (Kaposi-Sarkom-assoziiertes-Herpesvirus)
  Adenoviren

Parvovirus B19
Humane Papillomviren
Polyomaviren BK und JC
Merkelzell-Polyomavirus
Trichodysplasia spinulosa-Virus
Orthopoxviren
Parapoxviren
Picornaviren (Polio-, Coxsackie A/B-, Echo-, Rhinoviren)
Influenzaviren A und B
Spezifischer Nachweis der Hämagglutinin-Gene von Influenza A H1N1pdm2009, saisonaler Influenza A H3 sowie aviärer Influenza A H5 und H7
Parainfluenzaviren 1-4
Respiratory-Syncytial-Virus
Enteroviren
Parechoviren
Rhinoviren
Metapneumoviren
Coronaviren (OC43, 229E, NL63 und HKU1, MERS-Coronavirus)
Mumpsvirus
Rubellavirus
Astroviren
Noroviren Genogruppe 1 und 2
Rotaviren
Chikungunya-Virus
Denguevirus
FSME-Virus
West-Nil-Virus
Zikavirus
HIV-1 und HIV-2
HTLV-1 und HTLV-2
Hepatitis-A-Virus
Hepatitis-B-Virus
Hepatitis-C-Virus
Hepatitis-Delta-Virus
Hepatitis-E-Virus

- **Genotypisierungen** und **Tropismusbestimmungen**
  Genotyping and **testing of viral tropism**
  Adenovirus-Typisierung (Sequenzanalyse)
  Enterovirus-Typisierung (Sequenzanalyse)
  HBV-Genotypisierung (Sequenzanalyse)
  HCV-Genotypisierung (Sequenzanalyse)
  HIV-1- und HIV-2-Subtypisierung (Sequenzanalyse)
  Bestimmung des Korezeptor-Tropismus von HIV-1 durch Sequenzanalyse
  HPV-Typisierung (typspezifische PCR und Sequenzanalyse)

■ **Untersuchungen zum Nachweis von Resistenzen gegen Virostatika**
Antiviral drug resistance testing
Genotypische Resistenzbestimmung für HIV-1 durch Sequenzierung und Analyse des Mutationsprofils
- Proteaseinhibitoren
- Reverse Transkriptase-Inhibitoren
- Integrase-Inhibitoren
- Fusionsinhibitoren

Genotypische Resistenzbestimmung für HBV durch Sequenzierung und Analyse des Mutationsprofils
Genotypische Resistenzbestimmung (Ganciclovir) für CMV durch Sequenzierung des UL97-Gens und Analyse des Mutationsprofils
Genotypische Resistenzbestimmung (Aciclovir) für HSV-1 durch Sequenzierung des Thymidinkinase-Gens und Analyse des Mutationsprofils

Auf Anfrage stellen wir Ihnen gerne unsere „Hinweise für die Einsender“ und ein ausführliches Leistungsspektrum zur Verfügung.

Probenaufkommen und besondere Entwicklungen

In den Jahren 2017 und 2018 ist die Zahl der bearbeiteten Proben nach einer Steigerung um über 50% in 2016 nochmals um 10% (2017) bzw. 5% (2018) gegenüber dem jeweiligen Vorjahr angestiegen. Für diesen weiteren Anstieg sind im Wesentlichen noch die in den Vorjahren bereits begonnenen Entwicklungen (ab November 2015 Untersuchungen von Wangenschleimhaut-Abstrichen von Neugeborenen im Rahmen einer Studie zur Häufigkeit der konnatalen CMV-Infektion; ab Mai 2015 teilweise und ab Mai 2016 komplette Übernahme der serologischen Untersuchungen (vor allem Hepatitis- und HIV-Serologie) aus dem Zentrallabor des Universitätsklinikums) verantwortlich. Darüber hinaus war die Influenza-Saison 2017/2018 durch eine deutliche Steigerung der Einsendungen im Vergleich zu den vorhergehenden Jahren geprägt.

■ **Qualitätskontrolle und Akkreditierung**
Im Bereich der Qualitätskontrolle haben wir uns auch in den Jahren 2017 und 2018 am kompletten Programm der Ringversuche zur Virusserologie und Nukleinsäure-Diagnostik durch die nationale Organisation INSTAND e.V. beteiligt und auch an Pilot-Ringversuchen für neue Testparameter wie beispielsweise der Multiplex-Testung für respiratorische Viren mitgearbeitet. Darüber hinaus sind wir auch weiterhin als Referenzlabor an der Vortestung für die Ringversuche im Bereich HIV und HTLV, für die HEV-PCR und Norovirus-PCR tätig.
Nach der Begehung für die erfolgreiche dritte Reakkreditierung nach DIN EN ISO 15189:2014 im November 2016 fand im Mai 2018 eine Überwachungs-Begehung durch einen Fachgutachter statt. Dabei wurde unserem Diagnostik-Labor erneut eine hervorragende Arbeit bescheinigt.

■ **Der besondere Fall**
Bornavirus als Ursache einer fatalen Enzephalitis bei einem jungen Mann.
Nachdem im Herbst 2016 in der Neurologischen Universitätsklinik zwei Fälle von Enzephalitis mit tödlichem Ausgang bei jungen Patienten aufgetreten waren, bei denen sich trotz umfangreicher Diagnostik keine Ursache finden ließ, haben wir Mitte 2017 eine ungezielte Suche nach möglichen Krankheitserregern mittels Next Generation Sequencing aus formalin-

fixiertem Hirngewebe der beiden Patienten initiiert. Dabei fanden wir bei einem der beiden Patienten eine große Anzahl (etwa 10.000) Genomfragmente, die dem Virus der Bornaschen Erkrankung (klassisches Bornavirus, BoDV-1) zuzuordnen waren. Die Diagnose einer Bornavirus-Infektion konnte auch durch den RNA-Nachweis im Liquor mittels real-time-PCR, den Antigennachweis im Hirngewebe sowie den Nachweis einer Serokonversion für Bornavirus-Antikörper in zwei Serumproben des Patienten bestätigt werden. Dieser Fall wurde im Oktober 2018 im *New England Journal of Medicine* publiziert. In der gleichen Ausgabe wurde auch über ein Cluster von drei Bornavirus-Erkrankungen (zwei davon ebenfalls mit tödlichem Verlauf) bei Patienten berichtet, die Organe desselben Spenders transplantiert bekommen hatten. Inzwischen sind retrospektiv noch einige weitere Fälle von Bornavirus-Infektionen bei Patienten diagnostiziert worden, die seit den 1990er-Jahren an unklarer Enzephalitis verstorben sind. Die tatsächliche Häufigkeit solcher Erkrankungsfälle und auch die Frage, ob und ggf. wie häufig es auch weniger schwere oder asymptomatische Bornavirus-Infektionen gibt, muss jedoch noch geklärt werden.

Epidemiologische Aspekte

Respiratorische Viren. Die Einsendungen zum Nachweis respiratorischer Viren haben seit unserer Einführung der Mulitplex-Testung für ein breites Panel von respiratorischen Viren im Jahr 2013 kontinuierlich zugenommen und im Jahr 2018 wurden erstmals mehr als 2.000 Proben mit der Multiplex-PCR getestet. Um in den Wintermonaten gerade für die Notaufnahmen ein schnelleres Feedback für positive Influenza-Ergebnisse zu erreichen, haben wir seit der Saison 2017/2018 zusätzlich einen Influenza/RSV-real-time-PCR-Test eingeführt, der im Gegensatz zur batchweisen einmal täglichen Abarbeitung des Multiplex-Tests und der *in-house*-Influenza-PCR als *random-access*-Test eine umgehende Testung der eingehenden Proben ermöglicht. Mit beiden Tests zusammen sowie einem kleinen Anteil an *in-house*-PCR-Testung kamen wir für 2018 auf gute 3.000 Proben mit einer Positivrate von 33% im gesamten Jahr. Eine Aufschlüsselung nach den einzelnen Erregern zeigt die Abbildung 1. In der Saison 2017/2018 fiel eine starke Dominanz von Influenza-B-Viren (insgesamt 321 Nachweise) auf. Daneben war, wie in den Jahren 2014 und 2016, auch in 2018 wieder eine relativ hohe Zahl von Metapneumovirus (HMPV)-Infektionen zu verzeichnen (56 Fälle im Vergleich zu 18 Fällen im Jahr 2017).

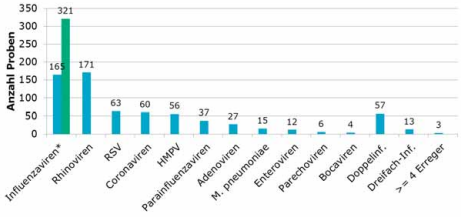

Abb. 1: Ergebnisse der Untersuchungen auf respiratorische Viren im Jahr 2018.
Positive Proben insgesamt: 1012/3048 (33,2%).

FSME. Die Diagnostik der FSME stützt sich im Gegensatz zu den anderen bei uns relevanten viralen ZNS-Infektionen wie Enterovirus- und Herpesvirus-Infektionen nicht primär auf den direkten Erregernachweis mittels PCR im Liquor, sondern auf den serologischen Nachweis von IgM- und IgG-Antikörpern im Serum sowie gegebenenfalls einer virusspezifischen intrathekalen Antikörperproduktion. Bei etwa 3-10 Fällen von serologisch gesicherter FSME-Erkrankung pro Jahr war es uns auch bisher in keinem Fall gelungen, FSME-RNA im Liquor nachzuweisen. Dies gelang uns erstmals im August 2016, wobei bei diesem Patienten zugleich die FSME-Antikörpertests negativ waren. Zweifel hinsichtlich der Spezifität des PCR-Befundes konnten dadurch entkräftet werden, dass eine Liquorprobe des Patienten in einem anderen Labor sowie eine Folgeprobe in unserem Labor ebenfalls

positiv auf FSME-RNA getestet wurden. Als Ursache für diese Diskrepanz kristallisierte sich heraus, dass der Patient mit dem B-Zell-depletierenden Antikörper Rituximab behandelt worden war, so dass eine Immunantwort auf die FSME-Infektion offensichtlich nicht zustande kam. In den folgenden 12 Monaten konnten wir die gleiche Konstellation aus positivem FSME-RNA-Nachweis und fehlender FSME-Antikörper-Reaktion bei zwei weiteren Patienten beobachten, die beide ebenfalls mit Rituximab behandelt worden waren. Bei allen „normalen“ FSME-Fällen blieben die PCR-Testungen weiterhin negativ, auch in solchen Fällen, die offensichtlich sehr früh diagnostiziert wurden, weil sie initial nur einen positiven IgM-Antikörpernachweis hatten und eine IgG-Serokonversion erst später nachgewiesen wurde. Diese Besonderheit gilt es daher zu berücksichtigen, wenn Patienten nach Rituximab-Therapie mit der Symptomatik einer Meningitis oder Enzephalitis auffällig werden.

Enteroviren und Parechoviren. Im Jahr 2017 erhielten wir seit dem Start im Jahr 2005 die dritthöchste Anzahl von Proben im Rahmen des LaNED-Labornetzwerks für die Enterovirus-Diagnostik. Die Positivrate war mit 27,4% jedoch deutlich niedriger als in den Jahren 2008 (57,7%) und 2013 (66,7%), in denen wir die bisher höchsten Zahlen an Einsendungen hatten. Von den nachgewiesenen Virustypen dominierte 2017 Echovirus 18, was hauptsächlich durch einen Ausbruch in einer Kindertagesstätte bedingt war. Neben den dort betreuten Kindern erkrankten in diesem Rahmen auch einzelne Erwachsene. 2018 waren die Zahl der Einsendungen und auch die Positivrate mit 20,4% nochmals niedriger. Auffällig war, dass nach Echovirus 30, einem in früheren Jahren schon häufig gefundenen Erreger, mit Coxsackievirus A6 ein Virus der Spezies A an zweiter Stelle in der Häufigkeit rangierte, das bisher hauptsächlich als Erreger der Hand-, Fuß-, Mundkrankheit und weniger als Meningitis-Erreger in Erscheinung getreten ist.

Darüber hinaus fanden wir 2018 in unseren Einsendungen erstmals eine Häufung von Parechovirus-Infektionen mit insgesamt 10 Fällen bei Kindern von unter 2 Jahren. Die ersten Fälle betrafen Neugeborene mit einem relativ schweren Erkrankungsbild im Sinne einer Neugeborenen-Sepsis, was zu einer gewissen Beunruhigung führte. Dass es sich hier nicht um einen nosokomialen Ausbruch handelte, war schon deshalb offensichtlich, weil die Kinder alle bereits krank in die Klinik kamen. Zudem konnten wir durch Sequenzanalysen auch rasch nachweisen, dass schon bei den initialen Fällen zwei verschiedene Parechovirus Typen (PeV3 und PeV5) nachweisbar waren und auch innerhalb eines Typs die Sequenzen bis auf jeweils zwei Fälle deutliche Unterschiede aufwiesen. Einige Wochen später kamen dann noch zwei Fälle von Parechovirus-1-Infektionen hinzu, die sich in ihrer Sequenz ebenfalls deutlich unterschieden. Interessanterweise waren diese beiden Kinder mit 10 bzw. 19 Monaten deutlich älter als die Kinder mit Parechovirus 3- und Parcheovirus-5-Infektionen, die alle weniger als 3 Monate alt waren (9-73 Tage bei stationärer Aufnahme). Glücklicherweise sind alle Fälle letzten Endes gutartig und ohne Folgeschäden verlaufen.

Hantaviren. Verglichen mit Regionen wie der Schwäbischen Alb, dem Bayerischen Wald oder dem Spessart sind Hantavirus-Infektionen in unserem Einzugsgebiet eine Seltenheit. Lediglich in den Jahren, wo deutschlandweit über 2.000 Fälle registriert wurden (2010 und 2012), wurden auch bei uns zwischen 5 und 10 Fällen diagnostiziert. Insofern war das Jahr 2017 – bundesweit mit etwas über 1.700 Fällen das Jahr mit der bisher dritthöchsten Zahl an Meldungen – mit insgesamt 13 Fällen von Hantavirus-Infektionen auch für uns sehr ungewöhnlich. Alle Fälle traten zwischen Anfang April und Ende August auf, wobei

zwei Häufungen mit vier bzw. fünf Fällen zwischen dem 25.04. und 05.05. sowie zwischen dem 21.07. und 08.08. auffielen. Wie bei Hantavirus-Infektionen üblich überwog das männliche Geschlecht mit 11 der 13 Fälle deutlich. Die Altersverteilung war aber mit 9 Personen unter 45 Jahren anders als deutschlandweit, wo die höchste Inzidenz 2017 bei den 50-59-Jährigen beobachtet wurde. Im Jahr 2018 lag die Zahl der diagnostizierten Hantavirus-Fälle dann wieder bei nur noch zwei, wobei diese auffälligerweise beide erst spät im Jahr (Mitte November und Mitte Dezember) auftraten.

Trends and particular events in viral diagnostics

In the years 2017 and 2018, the number of samples submitted to our diagnostic laboratory increased by a further 10% and 5%, respectively after the largest-ever increase of more than 50% in the year 2016. This further increase was still mainly due to the two changes that had already started earlier (from November 2015 onwards testing of buccal swab samples from newborns for a study on congenital CMV infection, from May 2015 partial and from May 2016 complete takeover of the infectious disease serology (mainly tests for hepatitis viruses and HIV) from the central clinical chemistry laboratory of the university hospital). Furthermore, the 2017/2018 influenza season was characterized by an extraordinarily high number of samples compared to previous years.

■ Quality control and accreditation

Also in 2017 and 2018, we continuously participated in the complete quality control program of the national QC organization INSTAND e.V., both for serology and for detection of viral nucleic acids. Additionally, we were also active in a number of pilot trials for quality control like multiplex testing for respiratory viruses. Furthermore, we continued to work as a reference laboratory for the pretesting of samples for the QC trials in HIV and HTLV serology as well as for the PCR programmes for HIV-1, HIV-2, hepatitis E virus and norovirus.

After the successful third re-accreditation of our diagnostic laboratory according to DIN EN ISO 15189:2014 in November 2016, we had one interim inspection in May 2018, when the auditor again complimented our laboratory for its excellent work.

■ A case of particular interest

Borna disease virus as cause of fatal encephalitis in a young man.

In autumn of 2016, two fatal cases of encephalitis occurred in young men in our university hospital, where no underlying cause could be found despite of extensive diagnostic efforts. Therefore, we started a search for potential pathogens in formalin-fixed brain tissue of both patients using next-generation sequencing. Introducing this approach, we found a large number (about 10,000) genome fragments corresponding to Borna disease virus (BoDV-1). The diagnosis of Bornavirus infection could be further confirmed by the detection of viral RNA in the CSF using real-time PCR, immunohistochemical detection of Bornavirus antigen in brain tissue and demonstration of seroconversion for Bornavirus antibodies in two serum samples from the patient. This case report was published in October 2018 in the New England Journal of Medicine. In the same issue, another report was published describing a cluster of three cases of Bornavirus encephalitis (two of them fatal) in patients who had received solid organ transplants from the same donor. Meanwhile, a number of other cases of Bornavirus infection have been diagnosed retrospectively in patients who died from encephalitis during the last 25 years. The actual frequency of such cases as well as the question if there are also less severe or

asymptomatic Bornavirus infections in humans still has to be investigated.

Epidemiological aspects

Respiratory viruses. Since the introduction of multiplex PCR for a broad spectrum of respiratory viruses in 2013, the number of samples submitted for this assay has continuously increased and reached 2,000 samples per year in 2018. In addition to this multiplex testing, which is carried out in a batchwise mode once daily, we have introduced a random-access test for influenza and RSV in the 2017/2018 influenza season to enable a faster feedback especially for the emergency departments. With these two assays and some in-house PCR testing for influenzaviruses, we reached over 3,000 samples with a positivity rate of 33% in 2018. Figure 1 shows the distribution of the detected pathogens. In the 2017/2018 season, there was a clear dominance of influenza B viruses with a total of 321 positive samples. Besides this, we also observed a relatively high number of metapneumovirus (HMPV) infections (56 cases compared to 18 cases in 2017), similar to the years 2014 and 2016.

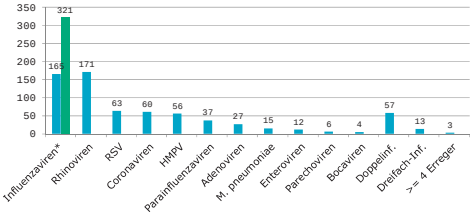

Figure 1: Results of PCR testing for respiratory viruses in 2018.
Total number of positive samples: 1012/3048 (33.2%)

Tick-borne encephalitis. In contrast to most other important pathogens of viral CNS infections like enteroviruses and herpesviruses, diagnosis of tick-borne encephalitis (TBEV) does not primarily rely on the detection of viral nucleic acid in CSF, but rather on the detection of IgM and IgG antibodies in serum and eventually also the detection of TBEV-specific intrathecal antibody synthesis. Actually, we never succeeded in the detection of TBEV RNA in CSF among the 3-10 patients with serologically confirmed TBE that we observe per year. The first detection of TBEV RNA in a CSF sample was in August 2016, and this was in a patient with negative antibody tests for TBEV. Doubts about the specificity of the PCR result could be disproved by the fact that a CSF sample from the same patient was tested positive for TBEV RNA in another laboratory and that a follow-up CSF sample in our lab was also positive for TBEV RNA. The reason for this discrepancy between virus detection and the lack of antibody production obviously was treatment with rituximab, a B cell-depleting monoclonal antibody. In the following 12 months, we found the same combination of positive TBEV RNA and negative antibody response in two other patients, who had both also been treated with rituximab. Among the “normal” TBE cases, PCR testing of the CSF remained negative, even in cases that were diagnosed early and had only IgM antibodies detectable in the first serum sample and IgG seroconversion was detected later on. This particularity has to be kept in mind when patients after treatment with rituximab present with symptoms of meningitis or encephalitis.

Enteroviruses and parechoviruses. In 2017, we received the third highest number of samples for enterovirus detection in the LaNED laboratory network since the start of this project in 2005. However, the positivity rate of 27.4% was rather low compared to the two years with the highest number of samples (2008: 57.7% and 2013: 66.7%). Among the virus types detected in 2017, echovirus 18 was most frequent. This was mainly due to an outbreak in a kindergarten, which included also a few adults who developed symptoms of meningitis. In 2018, the number of samples was somewhat lower and also the positivity rate further decreased to 20.4%. With respect to the distribution of virus types, it was remarkable that the

second most frequent type after echovirus 30, which has been frequently detected in previous years, was now Coxsackievirus A6. This serotype has up to now been noticed mainly as a cause of hand-, foot- and mouth disease, but not as a cause of viral meningitis.

Another peculiarity in 2018 was the observation of a cluster of parechovirus infections with a total number of 10 cases in children less than 2 years of age. The first cases were in newborns with relatively severe sepsis-like illness, which led to some degree of concern. However, since all newborns were already sick when they were admitted to the hospital, it was clear that this was not a nosocomial outbreak. Furthermore, we rapidly found out by sequencing that already among these initial cases two parechovirus types (PeV3 and PeV5) were circulating and that also within each type, the sequences were significantly different from each other except for two cases among each type. A few weeks later, we found two cases in which parechovirus 1 was detected, both again clearly different from each other. Interestingly, the two PeV1 cases were 10 and 19 months old and thus a lot older than the PeV3 and PeV5 cases, which were all younger than 3 months (9 and 73 days when admitted to the hospital). Fortunately, the clinical course in all patients was finally rather benign and no sequelae were observed.

■ ***Hantaviruses.*** Compared to regions like the Swabian Alb or the Bavarian forest, hantavirus infections are quite rare in our area. Only in those years when extraordinarily high numbers of more than 2,000 cases were reported in Germany (2010 and 2012), we also had a handful of cases in our submissions. Insofar, the number of 13 hantavirus cases that we observed in 2017 was very remarkable. All of the cases occurred between April and August, with two clusters of four and five cases between April 25 and May 5, and between July 21 and August 8, respectively. As usual in hantavirus infections, there was a strong preponderance for males with 11 out of the 13 cases. The age distribution, however, was quite different from that found in Germany as a whole, since 9 of the 13 patients were younger than 45 years, whereas in the nationwide reporting, the highest incidence was observed in the age group of 50-59 years. In 2018, the number of hantavirus cases diagnosed declined to two again, and interestingly both of these cases occurred unusually late in the year (mid-november and mid-december).

Ausgewählte Publikationen/ Selected References

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- Ruegamer, T., Hoffmann, R., Rohrhofer, A., Audebert, F., Salzberger, B., Korn, K., Schuster, P., Eichler, J., Schmidt, B. (2018). Inhibition of HIV-1 infection by human pegivirus type 1-derived peptides is affected by human pegivirus type 1 genotype and HIV-1 coreceptor tropism. AIDS. 32(14): 1951-1957. doi:10.1097/QAD.0000000000001926.

- Steininger, P.A., Bobinger, T., Dietrich, W., Lee, D.H., Knott, M., Bogdan, C., Korn, K., Lang, R. (2017). Two Cases of Severe Tick-Borne Encephalitis in Rituximab-Treated Patients in Germany: Implications for Diagnosis and Prevention. Open Forum Infect Dis. 4(4): ofx204. doi: 10.1093/ofid/ofx204.

- Bartenhagen, C., Fischer, U., Korn, K., Pfister, S.M., Gombert, M., Chen, C., Okpanyi, V., Hauer, J., Rinaldi, A., Bourquin, J.P., Eckert, C., Hu, J., Ensser, A., Dugas, M., Borkhardt, A. (2017). Infection as a cause of childhood leukemia: virus detection employing whole genome sequencing. Haematologica. 102(5): e179-e183. doi:10.3324/haematol.2016.155382.

- Steininger, P.A., Strasser, E.F., Ziehe, B., Eckstein, R., Rauh, M. (2017). Change of the metabolomic profile during short-term mononuclear cell storage. Vox Sang. 112(2):

163-172.
doi: 10.1111/vox.12482.

- Goerig, N.L., Frey, B., Korn, K., Fleckenstein, B., Überla, K., Schmidt, M.A., Dörfler, A., Engelhorn, T., Eyüpoglu, I., Rühle, P.F., Putz, F., Semrau, S., Gaipl, U.S., Fietkau, R. (2016). Frequent occurrence of therapeutically reversible CMV-associated encephalopathy during radiotherapy of the brain. Neuro Oncol. 18(12): 1664-1672.

- Böttcher, S., Obermeier, P.E., Neubauer, K., Diedrich, S., Laboratory Network for Enterovirus Diagnostics. (2016). Recombinant Enterovirus A71 Subgenogroup C1 Strains, Germany, 2015. Emerg Infect Dis. 22(10): 1843-1846.
doi: 10.3201/ eid2210.160357.

G. Drittmittelprojekte in der Übersicht
Survey of Funded Projects

Verbundforschung

Research Networks

DFG-Sonderforschungsbereich 796 "Steuerungsmechanismen mikrobieller Effektoren in Wirtszellen"

German Research Foundation, Collaborative Research Centre 796 „Reprogramming of host cells by microbial effectors"

Förderer: Deutsche Forschungsgemeinschaft
Sprecher: Prof. Uwe Sonnewald,
Lehrstuhl für Biochemie, Staudtstrasse 5, 91058 Erlangen
http://www.sfb796.de/

II. Förderperiode: 01.01.2013 – 31.12.2016
Auslauffinanzierung bis 31.12.2017

- **Projektbereich A: Structural basis of molecular interaction**
- **Projektbereich B: Reprogramming cellular processes**
- **Projektbereich C: Replication structures and transport**
- **Projektbereich Z: Analytics & Imaging**

Aktuell werden folgende Projekte des Instituts gefördert:

Teilprojekt B1
STAT-Activation in T-cell growth transformation
Teilprojektleiter: Prof. Armin Ensser

Teilprojekt B3
Interference of the viral effector proteins pp71 and IE1 with ND10-mediated intrinsic immunity against human cytomegalovirus infections
Teilprojektleiter: Prof. Thomas Stamminger

Teilprojekt C3
Regulation of the cytomegalovirus nuclear egress through a viral-cellular multiprotein complex
Teilprojektleiter: Prof. Manfred Marschall

Teilprojekt C6
Effects of Tax and p8 proteins on cell-to-cell transmission of Human T-cell lymphotropic virus type 1 (HTLV-1)
Teilprojektleiterin: Dr. Andrea Thoma-Kreß

- **DFG-Sonderforschungsbereich Transregio (TRR) 130 „B cell: Immunity and Autoimmunity“**
- **German Research Foundation, Transregio (TRR) 130 „B cell: Immunity and Autoimmunity”**

Förderer: Deutsche Forschungsgemeinschaft
Sprecher: Prof. Lars Nitschke, Department Biologie, Lehrstuhl für Genetik
http://www.trr130.forschung.uni-erlangen.de/index.php/en/home.html

Förderperiode: 01.07.2013 – 30.06.2017

Teilnehmende Institutionen:

- **Friedrich-Alexander Universität Erlangen-Nürnberg (coordinating university)**
- **Charité, Deutsches Rheuma-Forschungszentrum, Max-Planck-Institut für Infektionsbiologie**
- **Albert-Ludwigs-Universität Freiburg**
- **Universitätsmedizin Göttingen**

Es wurde folgendes Projekt des Instituts gefördert:

Teilprojekt 21
Verbesserung der HIV Env Antikörperantwort durch intrastrukturelle Hilfe von heterologen T-Helfer-Zellen
Teilprojektleiter: Prof. Klaus Überla

- **DFG-Graduiertenkolleg (GRK) 1949 „Immunantwort in Infektionskrankheiten – Regulation zwischen angeborener und erworbener Immunität“**
- **German Research Foundation, Research Training Group 1949 „Immune response in infectious diseases-Regulation between Innate and Adaptive Immunity”**

Förderer: Deutsche Forschungsgemeinschaft
Sprecher: Prof. Astrid Westendorf, Universitätsklinikum Essen, Institut für Medizinische Mikrobiologie
https://www.uni-due.de/grk1949/index.shtml

Förderperiode: 01.04.2014 – 30.09.2018

Teilnehmende Institutionen:

- **Universitätsklinikum Essen, Universität Duisburg-Essen (coordinating university)**
- **Universitätsklinikum Düsseldorf, Heinrich-Heine Universität Düsseldorf**
- **Ruhr-Universität Bochum**

Es wurden folgende Projekte gefördert:

Teilprojekt 5
Differential stimulation of innate immune responses by viral surface proteins modulating the antiviral antibody response
Teilprojektleiter: Prof. Klaus Überla, Prof. Matthias Tenbusch (Bochum)

Teilprojekt 13
Signal molecules of the innate immune response as adjuvants for gene-based vaccines
Teilprojektleiter: Prof. Matthias Tenbusch

- **EU - Europäische Union, EAVI 2020 – European AIDS Vaccine Initiative 2020**

- **EU – European Union, EAVI 2020 – European AIDS Vaccine Initiative 2020**

Förderer: European Commission – Directorate-General for Research & Innovation
Koordinator: Imperial College of Science, Technology and Medicine, London
http://www.eavi2020.eu/

Förderperiode: 01.11.2015 – 31.10.2020

Aktuell wird folgendes Projekt des Instituts gefördert:

Partner 14:
Universitätsklinikum Erlangen, Virologisches Institut
Projektleiter: Prof. Klaus Überla

- **CAVD – Collaboration on AIDS Vaccine Discovery**

https://www.cavd.org/

Vaccine discovery consortium "Antibodies without HIV T helper cells"

Förderer: Bill & Melinda Gates Foundation
Koordinator: Prof. Klaus Überla

Förderperiode: 17.08.2012 – 31.12.2019

Teilnehmende Institutionen:

- **Universitätsklinikum Erlangen, Virologisches Institut**
- **Deutsches Primatenzentrum (DPZ)**

■ ENB – Elitenetzwerk Bayern „Integrated Immunology“

■ ENB – Elitenetzwerk Bavaria “Integrated Immunology”

http://www.elitenetzwerk.bayern.de

Förderer: Bayerisches Staatsministerium für Wissenschaft und Kunst
Sprecher: Prof. Falk Nimmerjahn

Förderperiode: **01.10.2018 – 30.09.2023**

Aktuell wird folgendes Projekt des Instituts gefördert:

„Translational Immunology“
Teilprojektleiter: Prof. Klaus Überla

- **Interdisziplinäres Zentrum für Klinische Forschung (IZKF) der Medizinischen Fakultät: "Entzündungsprozesse: Genese, Diagnostik und Therapie"**

- **Interdisciplinary Center for Clinical Research of the Medical Faculty: "Inflammatory Processes: Ethiopathogenesis, Diagnostics and Therapy"**

Förderer: Bundesministerium für Bildung und Forschung, Projektträger Gesundheitsforschung

Förderperioden:

	6. Phase	**01.10.2013 – 30.09.2016**
	7. Phase	**01.01.2016 bzw. 01.07.2016 – 31.12.2019 bzw. 30.06.2020**

Sprecher: Prof. André Reis
Humangenetisches Institut, Universitätsklinikum Erlangen

http://www.izkf.med.uni-erlangen.de/

- **Projektbereich A: Infektionsforschung und Immunologie**
- **Projektbereich D: Schwerpunkt Tumorforschung**
- **Projektbereich E: Neurowissenschaften**
- **Projektbereich F: Nieren- und Kreislaufforschung**
- **Projektbereich J: Erstantragstellerprojekte**

Aktuell werden folgende Projekte des Instituts gefördert:

Phase 6, 01.10.2013 – 30.09.2016
Phase 7, flexibler Beginn: 01.01.2016 bis 01.07.2016

Teilprojekt A66
Identifizierung antiviraler Restriktionsfaktoren
Teilprojektleiter: Prof. Armin Ensser

Teilprojekt A67
TRIM5alpha inhibiert LINE-1 Retroelemente
Teilprojektleiter: Prof. Thomas Gramberg

Teilprojekt A70
DUB-Inhibitoren und HIV-1
Teilprojektleiter: Prof. Ulrich Schubert

Teilprojekt A71
Virale Modulation der Proteinkinase ULK1
Teilprojektleiter: Prof. Thomas Stamminger

Teilprojekt A73
Checkpoint Inhibitoren als Vakzinadjuvants
Teilprojektleiter: Prof. Klaus Überla

Teilprojekt J45
Modulation der PRC2 Aktivität durch HCMV IE2
Teilprojektleiter: Dr. Nina Reuter

Teilprojekt J57
Herpesviren und DUX4
Teilprojektleiter: Dr. Florian Full

Teilprojekt J69
Studying quality and sustainability of vaccine-induced T cell responses in ART-treated HIV infection
Teilprojektleiter: Dr. Christiane Krystelle Nganou Makamdop

Teilprojekt P008
Induction of mucosal immune responses by gene-based vaccines against viral respiratory tract infections
Teilprojektleiter: Prof. Matthias Tenbusch

Forschung in Einzelprojekten

Individual Grants

Deutsche Forschungsgemeinschaft (DFG)

German Research Foundation (DFG)

http://www.dfg.de/

„Relevanz von Fc-Effektorfunktionen für den Schutz vor Infektion der ersten Zelle im HIV-Primatenmodell“
Projektleiter: Prof. Klaus Überla
Voraussichtliche Dauer: 01.07.2018 – 30.06.2021
Finanzierung: DFG Ue 45/13-2

„Intrinsische Immunerkennung retroviraler Infektionen in SAMHD1 Knockout-Mäusen“
Projektleiter: Prof. Thomas Gramberg
Voraussichtliche Dauer: 01.09.2014 – 31.08.2017 – 28.02.2018
Finanzierung: DFG Gr 3355/3-1

„Die Rolle der Ephrin-A2 Rezeptor-Tyrosinkinase bei der Infektion mit dem Kaposi Sarkom-assoziierten Herpesvirus“
Projektleiter: PD Dr. Frank Neipel
Voraussichtliche Dauer: 01.07.2014 – 31.12.2017
Finanzierung: DFG Ne 740/2-1

„Mechanistische Untersuchungen zur antiviralen Wirkungsweise des Medikaments Artesunat und von optimierten synthetischen Derivaten“
Projektleiter: Prof. Manfred Marschall
Voraussichtliche Dauer: 01.09.2016 – 31.08.2019
Finanzierung: DFG Ma 1289/7-3

„Regulatorische Interaktion zwischen zellulären Zyklinen und dem Zyklin-abhängigen Proteinkinase-Ortholog pUL97 des humanen Cytomegalovirus“
Projektleiter: Prof. Manfred Marschall
Voraussichtliche Dauer: 01.07.2015 – 30.06.2018 – 31.08.2018
Finanzierung: DFG Ma 1289/8-1

„Die Peptidyl-Prolyl-Isomerase Pin1 als multifunktionaler Regulator der cytomegaloviralen Replikation“
Projektleiter: Dr. Jens Milbradt, Prof. Manfred Marschall
Voraussichtliche Dauer: 01.05.2017 – 30.04.2020
Finanzierung: DFG Mi 2143/2-1

„Erforschung des Cytomegalovirus-spezifischen nukleären Egresskomplexes als Target für die antivirale Therapie“
Projektleiter: Prof. Manfred Marschall
Voraussichtliche Dauer: 01.03.2018 – 28.02.2021
Finanzierung: DFG Ma 1289/11-1

■ **„Aufklärung der Virus-Wirt-Interaktion zur Inhibition der Transmission des Humanen T-Zell-Leukämievirus Typ 1 (HTLV-1)“**
Projektleiter: Dr. Andrea Thoma-Kreß
Voraussichtliche Dauer: 01.11.2017 – 31.10.2020
Finanzierung: DFG Th 2166/1-1

■ **„Gammaherpesvirale Tegumentproteine – wichtige Effektoren viraler Infektionen“**
Projektleiter: Prof. Armin Ensser
Voraussichtliche Dauer: 01.01.2018 – 31.12.2020
Finanzierung: DFG En 423/5-1

- **Europäische Union**
  Marie Sklodowska-Curie Actions

- **European Union**
  Marie Sklodowska-Curie Actions

http://ec.europa.eu/research/mariecurieactions/index_en.htm

Individual Fellowships (IF) – 703896-VAGPH2020-MSCA-IF – 2015

- **„The Viral Genome Associated Proteome“**

Projektleiter: Prof. Armin Ensser
Voraussichtliche Dauer: 01.02.2017 – 31.07.2019
Förderer: Europäische Kommission

Stiftungen

Foundations

Wilhelm Sander-Stiftung

Wilhelm Sander Foundation

http://www.sanst.de/

„Die CDK-ähnliche Proteinkinase pUL97 des Cytomegalovirus als Zielmolekül für die strukturbasierte Entwicklung einer neuen antiviralen Strategie"

Projektleiter: Prof. Manfred Marschall
Voraussichtliche Dauer: 01.10.2014 – 28.02.2017
Finanzierung: Wilhelm Sander-Stiftung 2011.085.2

„Virale Modulation des ATRX-Proteins – Bedeutung für die Interferonantwort und die Entstehung/Therapie maligner Tumore"

Projektleiter: Prof. Thomas Stamminger
Voraussichtliche Dauer: 01.01.2017 – 31.12.2018
(ab 01.07.2018 Transfer des Projekts an das Institut für Virologie der Universität Ulm)
Finanzierung: Wilhelm Sander-Stiftung 2016.087.1

BFHZ / CCUFB

Förderer: Bayerisch-Französisches Hochschulzentrum München

www.bayern-france.org

„Identification of host restriction factors against Human T-cell leukemia virus"

Projektleiter: Dr. Andrea Thoma-Kreß, Erlangen
Dr. Jean-Marie Pèloponèse, Montpellier
Voraussichtliche Dauer: 2014 – 2019

■ DAAD – Deutscher Akademischer Austauschdienst

■ DAAD – German Academic Exchange Service

http://www.daad.de

■ **German Egyptian Research Long-term Scholarship (GERLS) – Hassan Abdou Yousif Elsayed**

Projektleiter:	Prof. Klaus Überla
Dauer des Vorhabens:	2015 – 2017
Förderer:	Deutscher Akademischer Austauschdienst German Egyptian Research Long-term Scholarship (GERLS)

■ **PPP Programm Projektbezogener Personenaustausch Deutschland-Australien „Cytomegalovirus infection during pregnancy and transplantation"**

Projektleiter:	Prof. Manfred Marschall
Dauer des Vorhabens:	01.01.2017 – 31.12.2018
Förderer:	Deutscher Akademischer Austauschdienst (DAAD) Australian Go8 Funding (Go8)

■ STAEDTLER Stiftung Nürnberg

■ STAEDTLER Foundation Nürnberg

https://www.staedtler.de/de/stiftung

■ **„Adenoviren als Vektoren (Hilfsmittel) in der Gentherapie – Molekulargenetische Analysen"**

Projektleiter:	Prof. Walter Doerfler
Voraussichtliche Dauer:	2015 – 2016 – 2017 – 2018
Förderer:	Staedtler Stiftung Nürnberg

■ Johannes Frieda Marohn-Stiftung

■ Johannes Frieda Marohn Foundation

■ **„Cyclophilin"**

Projektleiter:	Dr. Jens Milbradt
Voraussichtliche Dauer:	16.06.2017 – 15.04.2018
Förderer:	Johannes Frieda Marohn-Stiftung Erlangen

■ **„SAMHD1, MCMV, intrinsic immunity"**

Projektleiter:	Prof. Thomas Gramberg
Voraussichtliche Dauer:	01.06.2018 – 31.05.2019
Förderer:	Johannes Frieda Marohn-Stiftung Erlangen

■ Boehringer Ingelheim Stiftung ■ Boehringer Ingelheim Foundation

https://www.boehringer-ingelheim-stiftung.de

■ **„A novel positive feedback loop in viral oncogenesis: Regulation of the viral tax oncoprotein by NF-kappa-B“**

Projektleiter: Dr. Andrea Thoma-Kreß
Voraussichtliche Dauer: 01.01.2018 – 31.03.2019
Förderer: Boehringer Ingelheim Stiftung

■ Doktor Robert Pfleger Stiftung Bamberg ■ Doctor Robert Pfleger Foundation Bamberg

https://www.pfleger-stiftung.de

■ **„Signalmoleküle der angeborenen Immunantwort als genetische Adjuvantien bei adenoviralen Vektorimmunisierungen gegen das Respiratorische Synzytial Virus (RSV)“**

Projektleiter: Prof. Matthias Tenbusch
Voraussichtliche Dauer: 01.07.2018 – 30.06.2019
Förderer: Doktor Robert Pfleger Stiftung Bamberg

Projektförderung Grants

National Institute of Health (NIH) USA

http://www.niaid.nih.gov/

„Congenital CMV and CNS infection mechanisms of protective immunity"
Projektleiter: Prof. Michael Mach
Voraussichtliche Dauer: 17.05.2017 – 30.04.2023
Förderer: National Institute of Health, USA, Bundesmittel

"Identification of pre-fusion conformers of HCMV gB"
Projektleiter: Prof. Michael Mach
Voraussichtliche Dauer: 01.07.2016 – 30.06.2018
Förderer: National Institute of Health, USA, Bundesmittel

"Global panel of non-human primate challenge viruses for standardized assessment of in vivo efficacy of HIV-1 Env antibodies"
Projektleiter: Prof. Klaus Überla
Voraussichtliche Dauer: 19.02.2018 – 31.01.2020
Förderer: National Institute of Health, USA, Bundesmittel

Qatar National Research Fund (QNRF)

"Prevalence determination and management of neonatal human cytomegalovirus infections and development of an identification, follow-up, and intervention program for associated hearing loss"
Projektleiter: Prof. Klaus Überla
Voraussichtliche Dauer: 18.11.2015 – 30.11.2018
Finanzierung: Qatar National Research Fund, Hamad Medical Corporation

Industrie | Industry

Projektleiter:	Prof. Ulrich Schubert
Förderzeitraum:	01.09.2006 – 31.10.2008 – 28.02.2012 – 30.09.2013 – 28.02.2015
Finanzierung:	**ViroLogik GmbH**
Projektleiter:	Prof. Ulrich Schubert
Förderzeitraum:	01.05.2011 – 30.04.2012 – 30.04.2013 – 30.09.2016 – 30.09.2019
Finanzierung:	**MetrioPharm AG**
Projektleiter:	Prof. Manfred Marschall
Förderzeitraum:	26.06.2017 – 16.09.2017; Nachbearbeitung bis dato 2019
Finanzierung:	**Immunic AG, Martinsried**

H. Publikationen
Publications

Beiträge zu Journalen / Scientific Journals

2017

Agarwal, N., Iyer, D., Gabbi, C., Saha, P., Patel, S.G., Mo, Q., Chang, B., Goswami, B., Schubert, U., Kopp, J.B., Lewis, D.E., Balasubramanyam, A. (2017). HIV-1 viral protein R (Vpr) induces fatty liver in mice via LXRα and PPARα dysregulation: implications for HIV-specific pathogenesis of NAFLD. *Scientific Reports* **7**, 13362.

Bartenhagen, C., Fischer, U., Korn, K., Pfister, S.M., Gombert, M., Chen, C., Okpanyi, V., Hauer, J., Rinaldi, A., Bourquin, J.P., Eckert, C., Hu, J., Ensser, A., Dugas, M., Borkhardt, A. (2017). Infection as a cause of childhood leukemia-virus detection employing whole genome sequencing. *Haematologica* **102**, e179–e183.

Bock, C.M., Parameshwarappa, G., Bönisch, S., Bauer, W., Hutterer, C., Leidenberger, M., Friedrich, O., Marschall, M., Kappes, B., Görling, A., Tsogoeva, S.B. (2017). Deeper Insight into the Six-Step Domino Reaction of Aldehydes with Malononitrile and Evaluation of Antiviral and Antimalarial Activities of the Obtained Bicyclic Products. *ChemistryOpen* **6**, 364–374.

Bongard, N., Lapuente, D., Windmann, S., Dittmer, U., Tenbusch, M., Bayer, W. (2017). Interference of retroviral envelope with vaccine-induced CD8+ T cell responses is relieved by co-administration of cytokine-encoding vectors. *Retrovirology* **14**, 28.

Bootz, A., Karbach, A., Spindler, J., Kropff, B., Reuter, N., Sticht, H., Winkler, T.H., Britt, W.J., Mach, M. (2017). Protective capacity of neutralizing and non-neutralizing antibodies against glycoprotein B of cytomegalovirus. *PLoS pathogens* **13**, e1006601.

Devos, F.C., Maaske, A., Robichaud, A., Pollaris, L., Seys, S., Lopez, C.A., Verbeken, E., Tenbusch, M., Lories, R., Nemery, B., Hoet, P.H., Vanoirbeek, J.A. (2017). Forced expiration measurements in mouse models of obstructive and restrictive lung diseases. *Respiratory Research* **18**, 123.

Fiebig, U., Holzer, A., Ivanusic, D., Plotzki, E., Hengel, H., Neipel, F., Denner, J. (2017). Antibody Cross-Reactivity between Porcine Cytomegalovirus (PCMV) and Human Herpesvirus-6 (HHV-6). *Viruses* **9**, 317.

Fröhlich, T., Reiter, C., Ibrahim, M.M., Beutel, J., Hutterer, C., Zeitträger, I., Bahsi, H., Leidenberger, M., Friedrich, O., Kappes, B., Efferth, T., Marschall, M., Tsogoeva, S.B. (2017). Synthesis of novel hybrids of quinazoline and artemisinin with high activities against plasmodium falciparum, human cytomegalovirus and leukemia cells. *ACS Omega* **2**, 2422−2431.

Full, F., Hahn, A.S., Grosskopf, A.K., Ensser, A. (2017). Gammaherpesviral Tegument Proteins, PML-Nuclear Bodies and the Ubiquitin-Proteasome System. *Viruses* **9**, 308.

Goerig, N.L., Frey, B., Überla, K., Gaipl, U., Fietkau, R. (2017). A clinician's plea to test glioma patients for CMV. *Neuro-Oncology* **19**, 1282–1283.

Hahn, F., Schmalen, A., Setz, C., Friedrich, M., Schlößer, S., Kölle, J., Spranger, R., Rauch, P., Fraedrich, K., Reif, T., Karius-Fischer, J., Balasubramanyam, A., Henklein, P., Fossen, T., Schubert, U. (2017). Proteolysis of mature HIV-1 p6 Gag protein by the insulin-degrading enzyme (IDE) regulates virus replication in an Env-dependent manner. *PLOS ONE* **12**, e0174254.

Heilingloh, C.S., Grosche, L., Kummer, M., Mühl-Zürbes, P., Kamm, L., Scherer, M., Latzko, M., Stamminger, T., Steinkasserer, A. (2017). The Major Immediate-Early Protein IE2 of Human Cytomegalovirus Is Sufficient to Induce Proteasomal Degradation of CD83 on Mature Dendritic Cells. *Front. Microbiol.* **8**, 119.

Held, F.E., Guryev, A.A., Fröhlich, T., Hampel, F., Kahnt, A., Hutterer, C., Steingruber, M., Bahsi, H., von Bojničić-Kninski, C., Mattes, D.S., Foertsch, T.C., Nesterov-Mueller, A., Marschall, M., Tsogoeva, S.B. (2017). Facile access to novel antiviral quinazoline heterocycles with fluorescence properties via merging metal-free domino reactions. *Nature Comm.* **8**, 15071.

Hutterer, C., Milbradt, J., Hamilton, S., Zaja, M., Leban, J., Henry, C., Vitt, D., Steingruber, M., Sonntag, E., Zeitträger, I., Bahsi, H., Stamminger, T., Rawlinson, W.D., Strobl, S., Marschall, M. (2017). Inhibitors of dual-specificity tyrosine phosphorylation-regulated kinases (DYRK) exert a strong anti-herpesviral activity. *Antiviral Res.* **143**, 113–121.

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Kongressbeiträge Abstracts

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Bootz, A., Karbach, A., Spindler, J., Sticht, H., Winkler, T., Kropff, B. , Reuter, N., Mach, M. Protective Capacity of Neutralizing and Non-neutralizing Antibodies against Glycoprotein B of Cytomegalovirus. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

Damm, D., Suleiman, E., Katinger, D., Wyatt, R., Temchura, V., Überla, K. Activation of transgenic T and B cells by liposomal vaccines encapsidating heterologous T helper cell epitopes. *EAVI 2020 2nd Annual Meeting, Barcelona, 07.-08.11.2017.*

Doerfler, W., Weber, S., Naumann, A. Epigenetic consequences of foreign DNA insertions: A mechanism in oncogenesis? *The 2nd Tore Nilson/ Karolinska Institutet Conference, Nobel Forum, Stockholm, 27.-29.04.2017.*

Doerfler, W., Weber, S., Naumann, A. Epigenetic consequences of foreign DNA insertions: Beware of genome manipulations. *Epigenetics Conference, Institute of Molecular Biology, National Academy of Sciences, Yerevan, Armenia, 06.06.2017.*

Donhauser, N., Millen, S., Jeninga, M., Socher, E., Hofmann, J., Sticht, H., Thoma-Kress, A.K.. Composition of a "transport of p8 complex" (TOPC) to understand transfer of the HTLV-1 p8 protein to target cells. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

Elsayed, H., Temchura, V., Nabi, G., Tenbusch, M., Überla, K. Intrastructural help: harnessing pre-existing T helper cells induced by licensed vaccines to improve HIV-1 Env antibody responses to virus-like particle vaccines. *9th Autumn School "Current Concepts in Immunology". Merseburg, 08.-13.10.2017.*

Elsayed, H., Temchura, V., Nabi, G., Tenbusch, M., Überla, K. Intrastructural help: harnessing pre-existing T helper cells induced by licensed vaccines to improve HIV-1 Env antibody responses to virus-like particle vaccines. *47th Annual Meeting of the German Society for Immunology: Erlangen, 12.–15.09.2017.*

Frank, T., Niemann, I., Reichel, A., Scherer, M., Mahmoudian, S., Krenz, B., Hofmann, J., Biesinger, B., Sticht, H. The vGPCR pUS27 of HCMV induces the expression of chemoattractant cytokines and is restrained by PDZ proteins regulating epithelial polarity. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

Full, F., van Gent, M., Sparrer, K.M.J., Walter, S., Scherer, M., Stürzl, M., Korn, K., Stamminger, T., Ensser, A., Gack, M.U. TRIM43 restricts KSHV infection by regulating centrosome integrity. *20th International Workshop on KSHV and Related Agents, Berlin, 25.-28.07.2017.*

Full, F., Hahn, A., Grosskopf, A., Scholz, B., Jungnickl, D., Ensser, A. Proteasomal degradation of ND10 component SP100 by herpesvirus saimiri critically dependens on lysine 819 of viral FGARAT homolog ORF3. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

Full, F., Hahn, A., Grosskopf, A., Scholz, B., Jungnickl, D., Ensser, A. Proteasomal degradation of ND10 component SP100 by herpesvirus saimiri critically dependens on lysine 819 of viral FGARAT homolog ORF3. *20th International Workshop on KSHV and Related Agents, Berlin, 25.-28.07.2017.*

Grosskopf, A.K., Ensser, A., Schlagowski, S., Desrosiers, R.C., Hahn, A.S. A conserved Eph family receptor-binding motif and novel receptor interactions of the gH/gL complex of KSHV and RRV - determinants of infectivity and tropism. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

Grosskopf, A.K., Ensser, A., Schlagowski, S., Desrosiers, R.C., Hahn, A.S. A conserved Eph family receptor-binding motif and novel receptor interactions of the gH/gL complex of KSHV and RRV - determinants of infectivity and tropism. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

Grosskopf, A.K., Ensser, A., Schlagowski, S., Desrosiers, R.C., Hahn, A.S. A conserved Eph family receptor-binding motif and novel receptor interactions of the gH/gL complex of KSHV and RRV - determinants of infectivity and tropism. *20th International Workshop on KSHV and Related Agents, Berlin, 25.-28.07.2017.*

Hahn, A.S., Full, F., Grosskopf, A.K., Jungnickl, D., Scholz, B., Ensser, A. The Viral FGARAT Homologs of Rhadinoviruses Effect Proteasomal Degradation of ND10 Components. *EMBO Conference on Hijacking host signalling and epigenetic mimicry during infections. Institut Pasteur, Paris, 13.-16.06.2017.*

Hahn, A., Grosskopf, A., Full, F., Jungnickl, D., Scholz, B., Ensser, A. Gammaherpesviral tegument proteins - crucial effectors of viral infection. *Gordon Research Conference Viruses & Cells, Barga, Italy, 14.-19.05.2017.*

Hahn, A.S., Grosskopf, A.K., Full, F., Scholz, B., Jungnickl, D., Ensser, A. The Viral FGARAT Homologs of Rhadinoviruses Effect Proteasomal Degradation of ND10 Components. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

Herrmann, A., Behrendt, R., Wittmann, S., Roers, A., Gramberg, T. SAMHD1-dependent retroviral restriction and sensing in mice. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

Herrmann, A., Wittmann, S., Shepard, C., Kim, B., Thomas, D., Ferreiros, N., Gramberg, T. The SAMHD1-mediated inhibition of LINE-1 is regulated by phosphorylation. *The Mobile Genome, EMBL, Heidelberg, 11.-14.11.2017.*

Klessing, S., Temchura, V., Überla, K. Optimizing the Memory B Cell Response by Intrastructural Help. *9th Autumn School "Current Concepts in Immunology", Merseburg, 08.-13.10.2017.*

Kolenbrander, A., Überla, K., Temchura, V. Generation of T follicular helper cells in double BCR/TCR-transgenic primary cell cultures. *19th International Conference on Lymphatic Tissues and Germinal Centres in Immune Reactions, Venice, 14.-17.09.2017.*

König, P, Feichtinger, S., Svrlanska, A., Stamminger, T. Inhibitors of the autophagy-initiating protein kinase Ulk1 interfere with HCMV replication. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

Lanfer, J., Fischer, M., Disch, A., Holzer, A., Neipel, F. The Ephrin A2 receptor tyrosin kinase (EphA2) is downregulated by the KSHV immediate-early transactivator RTA. *20th International Workshop on KSHV and Related Agents, Berlin, 25.-28.07.2017.*

Lapuente, D., Maaske, A., Stab, V., Bayer, W., Ehrhardt, C., Tenbusch, M. IL-1β as mucosal vaccine adjuvant: Specific induction of tissue-resident memory T cells and enhanced protection against heterologous IAV. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

Lapuente, D., Maaske, A., Stab, V., Bayer, W., Ehrhardt, C., Tenbusch, M. IL-1β as mucosal vaccine adjuvant: the specific induction of tissue-resident memory T cells leads to an enhanced protection against heterologous IAV. *47th Annual Meeting of the German Society for Immunology, Erlangen, 12.-15.09.2017.*

Millen, S., Gross, C., Mann, M.C., Überla, K., Thoma-Kress, A.K. Assessing the Role of the Novel Tax Targets COL4A1 and COL4A2 on Virus Transmission. *18th International Conference on Human Retrovirology – HTLV and Related Viruses, Tokyo, Japan, 07.-10.03.2017.*

Millen, S., Gross, C., Mann, M.C., Überla, K., Thoma-Kress, A.K. Spotting the effect on HTLV-1 transmission – COL4A1 and COL4A2 are novel targets of the Tax-1 oncoprotein. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

Reuter, N., Reichel, A., Scherer, M., Stamminger, T. SUMOylation of IE2p86 is Required for Efficient Autorepression of The Human Cytomegalovirus Major Immediate-Early Promoter. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

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Reichel, A., Scherer, M., Stilp, A.-C., Reuter, N., Lukassen, S., Winterpacht, A., Stamminger, T. Evidence for an inter-regulation of the chromatin remodeling factor SPOC1 and ND10 components in HCMV restriction. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

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Scherer, M., Strauch, V., Müller, R., Schilling, E.-M., Schweininger, J., Muller Y.A., Stamminger, T. Dissecting the Species-specific Interplay of PML Nuclear Bodies and the Cytomegalovirus IE1 Protein. *42nd Annual International Herpesvirus Workshop (IHW 2017), Ghent, Belgium, 29.07.-02.08.2017.*

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Setz, C., Friedrich, M., Rauch, P., Temchura, V., Traxdorf, M., Schubert, U. Antiretroviral therapy with amendment of HIV-1 specific T-cell response. *9th Cellular Therapy Symposium, Erlangen, Germany, 16.-17.03.2017.*

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Tannig, P., Temchura, V., Überla, K. Checkpoint inhibitors as adjuvants for viral vaccines. *9th Autumn School "Current Concepts in Immunology", Merseburg, 08.-13.10.2017.*

Thomas, M., Müller, R., Horn, G., Bogdanow, B., Selbach, M., Fossen, T., Stamminger, T. The second alpha-helix within pUL69 contains pUL97-phosphorylation sites that critically affect Pin1-mediated isomerization and efficient multiplication of HCMV. *42nd Annual International Herpesvirus Workshop, Ghent, Belgium, 29.07.-02.08.2017.*

Volkmann, B., Eissmann, K., Wittmann, S., Ross, J.J., Gramberg, T. TRIM5α blocks the replication of LINE-1 retroelements. *The Mobile Genome Meeting, EMBL, Heidelberg, 11.-14.11.2017.*

Volkmann, B., Herrmann, A., Wittmann, S., Ross, J.J., Gramberg, T. Comparison of retroviral restriction factors blocking LINE-1 retrotransposition. *27th Annual Meeting of the Society for Virology, Marburg, 22.-25.03.2017.*

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Bertz, S., Knöll, A., Stöhr, R., Büttner-Herold, M., Compérat, E., Gaisa, N., Karl, A., Horst, D., Wullich, B., Ensser, A., Hartmann, A. Integration of BK Polyoma virus in micropapillary urothelial carcinoma – A role for pathogenesis? *102. Jahrestagung der Deutschen Deutschen Gesellschaft für Pathologie, Berlin, 24.-26.05.2018.*

Damm, D., Suleiman, E., Katinger, D., Elsayed, H., Kolenbrander, A., Ingale, J., Wyatt, R., Nemazee, D., Temchura, V., Überla, K. Activation of transgenic T and B cells by liposomal vaccines encapsulating heterologous T helper cell epitopes. *28th Annual Meeting of the Society for Virology, Würzburg, 14.–17.03.2018.*

Deutschmann, J. A viral kinase counteracts in vivo restriction of murine cytomegalovirus by SAMHD1. *GFV-Workshop Immunobiology of Viral Infections, Tauberbischofsheim, 26.-28.09.2018.*

Deutschmann, J. SAMHD1 restricts the replication of murine cytomegalovirus and is counteracted by the viral kinase M97. *International Herpesvirus Workshop, Vancvouver, Canada, 21.-25.07.2018.*

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Doerfler, W., Weber, S., Naumann, A. Epigenetic re-programming of the host genome upon foreign (viral) DNA invasion into cells. *Shrimp Epigenome Project, 119th National Shellfisheries Association Annual Meeting, Seattle, WA, USA, 19.03.2018.*

Donhauser, N., Heym, S., Thoma-Kress, A.K. Quantitating the Transfer of the HTLV-1 p8 Protein between T-cells by Flow Cytometry. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Elsayed, H., Nabi, G., Mckinstry, W.J., Rice, J., Stevenson, F.K., Salazar, A.M., Tenbusch, M., Temchura, V., Überla, K. Harnessing T-helper (Th) cell responses induced by licensed vaccines for HIV vaccine development. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Elsayed, H., Nabi, G., Mckinstry, W.J., Tenbusch, M., Temchura, V., Überla, K. Harnessing T-helper cell responses induced by licensed vaccines for HIV vaccine development. *5th European Congress of Immunology, Amsterdam, 02.-05.09.2018.*

Ensser, A. Severe encephalitis caused by mammalian 1 bornavirus. *RNA Virus Persistence Meeting: Mechanisms and Consequences, Institute of Virology, Medical Center - University of Freiburg, 23.-25.08.2018.*

Ensser, A., Grosskopf, A., Mätz-Rensing, K., Roos, C., Hahn, A.S. Isolation and complete genomic sequence of a novel rhesus macaque foamy virus isolate with a serotype 1-like env. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Frank, T., Niemann, I., Reichel, A., Scherer, M., Mahmoudian, S., Krenz, B., Hofmann, J., Biesinger, B., Sticht, H., Stamminger, T. The vGPCR pUS27 of HCMV induces the expression of chemoattractant cytokines and is restrained by PDZ proteins regulating epithelial polarity. *13th Mini-Herpesvirus Workshop, Hamburg, Germany, 05.10.2018.*

Frank, T., Niemann, I., Reichel, A., Scherer, M., Mahmoudian, S., Krenz, B., Hofmann, J., Biesinger, B., Sticht, H., Stamminger, T. The vGPCR pUS27 of HCMV induces the expression of chemoattractant cytokines and is restrained by PDZ proteins regulating epithelial polarity. *43rd Annual International Herpesvirus Workshop, Vancouver, Canada, 21.-25.07.2018.*

Frank, T., Niemann, I., Reichel, A., Scherer, M., Mahmoudian, S., Krenz, B., Hofmann, J., Biesinger, B., Sticht, H., Stamminger, T. The vGPCR pUS27 of HCMV induces the expression of chemoattractant cytokines and is restrained by PDZ proteins regulating epithelial polarity. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Full, F., van Gent, M., Sparrer, K.M.J., Chiang, C., Zurenski, M.A., Scherer, M., Brockmeyer, N.H., Heinzerling, L., Sturzl, M., Korn, K., Stamminger, T., Ensser, A., Gack, M.U. TRIM43 restricts herpesviral infection by regulating centrosome integrity. *43rd Annual International Herpesvirus Workshop, Vancouver, Canada, 21.-25.07.2018.*

Full, F., Jungnickl, D., Teufert, N., Scholz, B., Ensser, A. CRISPR/Cas9 in Herpesvirology – viral genome localisation and genome wide screening for the identification of antiviral cellular restriction factors. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Full, F., Scholz, B., Jungnickl, D., Grosskopf, A., Hahn, A.S., Ensser, A. Restriction of Herpesviruses by Structural Maintenance of Chromosome Domain containing Proteins. *43rd Annual International Herpesvirus Workshop, Vancouver, Canada, 21.-25.07.2018.*

Gramberg, T. LINE-1 retroelements are blocked by SAMHD1 in cycling cells. *Retroviruses Meeting, Cold Spring Harbor 24.-30.05.2018.*

Grosskopf, A., Ensser, A., Schlagowski, S., Desrosiers, R.C., Hahn, A.S. The Rhesus Monkey Rhadinovirus Interacts Through gH with Plexin Domain Containing Protein 2, a Novel Cellular Receptor. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Grosskopf, A., Ensser, A., Schlagowski, S., Desrosiers, R.C., Hahn, A.S. The Rhesus Monkey Rhadinovirus Interacts Through gH with Plexin Domain Containing Proteins 1/2, a Novel Cellular Receptor Family. *43rd Annual International Herpesvirus Workshop, Vancouver, Canada, 21.-25.07.2018.*

Hahn, F., Fröhlich, T., Frank, T., Bertzbach, L.D., Kohrt, S., Kaufer, B.B., Stamminger, T., Tsogoeva, S.B., Marschall, M. Artesunate-derived monomeric, dimeric and trimeric experimental drugs – their unique mechanistic basis and pronounced antiherpesviral activity. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Herrmann, A., Wittmann, S., Shepard, C., Kim, B., Thomas, D., Ferreiros, N., Gramberg, T. SAMHD1 inhibits endogenous retroelements in a phospho-dependent manner. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Hrycak, C., Schöne, D., Windmann, S., Lapuente, D., Dittmer, U., Tenbusch, M., Bayer, W. Competition between adenoviral CD8+ T cell epitopes with transgene-derived epitopes abrogates transgene-specific CD8+ T cell. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Knöll, A., Bertz, S., Stöhr, R., Büttner-Herold, M., Compérat, E., Gaisa, N., Karl, A., Horst, D., Wullich, B., Hartmann, A., Ensser, A. Integration of BK Polyoma virus in micropapillary urothelial carcinoma – A role for pathogenesis? *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Lanfer, J., Holzer, A., Neipel, F. The Ephrin A2 receptor tyrosin kinase (EphA2) is downregulated by the KSHV immediate-early transactivator RTA. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Lapuente, D., Storcksdieck genannt Bonsmann, M., Maaske, A., Stab, V., Heinecke, V., Liedtke, K., Heß, R., Westendorf, A.M., Bayer, W., Ehrhardt, C., Tenbusch, M. Interleukin-1β paves the way for protective lung-resident memory T-cells: Implications for a universal influenza vaccine? *6th International Influenza Meeting, Münster, 02.-04.09.2018.*

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Millen, S., Gross, C., Mann, M.C., Überla, K., Thoma-Kress, A.K. The HTLV-1 induced Extracellular Matrix Protein COL4A2 is critical for Virus Processing and Release. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Millen, S., Wolf, L., Göttlicher, T., Schmitt, S., Fleckenstein, B., Thoma-Kress, A.K. A novel positive feedback loop between the HTLV-1 Tax oncoprotein and NF-κB activity in T-cells. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Reichel, A., Scherer, M., Stilp, A.-C., Reuter, N., Lukassen, S., Schreiner, S., Winterpacht, A., Stamminger, T. The chromatin remodeling factor SPOC1 restricts human cytomegalovirus (HCMV) by recruitment of the corepressor protein KAP-1 to the viral immediate early promoter. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Scherer, M., Reichel, A., Schilling, E.-M., Reuter, N., Müller, R., Stamminger, T. Entrapment of HCMV genomes in PML nuclear cages as a novel intrinsic host defense mechanism. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Svrlanska, A., Stamminger, T., Reuter, N. Polycomb repressive complex 1 and 2 contribute to HCMV DNA replication independent of their enzymatic activity. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Tannig, P., Beutel, J., Temchura, V., Überla, K., Eichler, J. Coupling of HIV-1 envelope proteins onto liposomes via coiled-coil mediated heterodimerization. *EAVI2020's 3rd Annual Meeting, Madrid, 18.-19.10.2018.*

Tannig, P., Temchura, V., Lapuente, D., Tenbusch, M., Überla, K. Checkpoint inhibitors as adjuvants for viral vaccines. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03. 2018.*

Volkmann, B. TRIM5α blocks the replication of LINE-1 retroelements. *GFV-Workshop Immunobiology of Viral Infections, Tauberbischofsheim, 26.-28.09.2018.*

Volkmann, B., Wittmann, S., Biesinger, B., Gramberg, T. AP-1 signaling regulates LINE-1 retrotransposition. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Walter, S., Gack, M.U., Ensser, A., Full, F. The role of DUX4 in herpesviral infection. *International Herpesvirus Workshop, Vancvouver, Canada, 21.-25.07.2018.*

Walter, S., Gack, M.U., Ensser, A., Full, F. The role of DUX4 in herpesviral infection. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Xiao, H., Grewe, B., Ensser, A., Beatriz-Villela, A., Überla, K. A genome-wide CRISPR screen to identify cellular factors regulating Rev-dependent gene expression of HIV-1. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Xiao, H., Grewe, B., Villela, A.B., Ensser, A., Überla, K. A genome-wide CRISPR screen to identify cellular factors regulating Rev-dependent gene expression of HIV-1. *28th Annual Meeting of the Society for Virology, Würzburg, 14.-17.03.2018.*

Buch- und Übersichtsartikel

Books and Reviews

2017

Doerfler, W. (2017). Discoveries in Molecular Genetics with the Adenovirus 12 System: Integration of Viral DNA and Epigenetic Consequences. *In: Epigenetics of Infectious Diseases. Doerfler, W., Casadasús, J., and Noyer-Weidner, M. (eds.).* Springer-Verlag, Cham, Heidelberg, New York, Dordrecht, London, pp. 47–63.

Doerfler, W. (2017). Zum Diskurs zwischen Theologie und Naturwissenschaft - Perzeptionen aus dem Universum? *In: den Hertog, G., Heuser, S., Hofheinz, M., and Wannenwetsch, B. (eds.), Sagen, was Sache ist. Versuche explorativer Ethik. Festausgabe zu Ehren von Hans G. Ulrich*, Evangelische Verlagsanstalt, Leipzig, pp. 273–290.

Doerfler, W., Casadesús, J., Noyer-Weider, M. (eds.) (2017). *Epigenetics of Infectious Diseases.* Springer-Verlag, Cham, Heidelberg, New York, Dordrecht, London.

Gross, C., Thoma-Kress, A.K. (2017). Reporter Systems to Study HTLV-1 Transmission. *In: Methods in Molecular Biology (Clifton, N.J.),* **1582**, pp. 33–46.

Manicone, M., Rende, F., Cavallari, I., Thoma-Kress, A.K., Ciminale, V. (2017). Expression of HTLV-1 Genes in T-Cells Using RNA Electroporation. *In: Methods in Molecular Biology (Clifton, N.J.),* **1582**, pp. 155–170.

Scherer, M., Schilling, E.-M., Stamminger, T. (2017). The Human CMV IE1 Protein: An Offender of PML Nuclear Bodies. *In: Cell Biology of Herpes Viruses*, Springer-Verlag, p. 77–94.

Externe Vorträge (ohne Kongressbeiträge mit Abstrakt)

Presentations (without abstract)

Prof. Walter Doerfler

16.03.2017 Epigenetics of virus infections and viral oncogenesis
Tele-Conference "One Health Epigenomics and Microbiomes", Framingham, MA, USA

24.01.2018 Epigenetic re-programming upon foreing (viral) DNA invasion into cells.
Biomedicum, Medical Faculty Uppsala Universitet, Uppsala, Sweden

29.05.2018 Epigenetik – ein etwas anderer Blick auf die Genetik
Fakultäten-Club, Universität Erlangen-Nürnberg

14.10.2018 Genetically manipulated organisms (GMO's) – Epigenetic consequences of foreign DNA insertions
Ventnor Foundation Alumni, Emden, Hilton S. Read Lecture

Prof. Armin Ensser

14.06.2018 CRISPR/Cas9 - Präzisionswerkzeuge für Biologie und Medizin
Collegium Alexandrinum, Friedrich Alexander Universität Erlangen-Nürnberg

Prof. Thomas Gramberg

08.05.2017 The role of SAMHD1 in fending off Retroviruses and endogenous Retroelements
Robert Koch Institut, Berlin

08.06.2017 The role of SAMHD1 in fending off Retroviruses and endogenous Retroelements
Institute of Virology, Hannover Medical School

25.05.2018 LINE-1 retroelements are blocked by SAMHD1 in cycling cells
Cold Spring Harbor Laboratories, NY, USA

Dr. Klaus Korn

04.04.2017 Virologische Diagnostik – ein Update
Interdisziplinäre Fortbildung Hämatologie/Onkologie, Kinderklinik Erlangen

09.12.2017 Multiplex-PCR und andere kulturunabhängige Schnellverfahren: Atemwegsinfektionen
Klinisch-Mikrobiologisch-Infektiologisches Symposium, Berlin

26.09.2018 Severe encephalitis caused by mammalian 1 orthobornavirus
21st ESCV Annual Meeting, Athen

09.11.2018 EBV-Dual-Target-PCR
Laborleitertreffen der virologischen Universitätsinstitute, Würzburg

10.11.2018 Tödliche Enzephalitis durch „mammalian 1 orthobornavirus“ (klassisches Bornavirus)
Tagung des Arbeitskreises „Klinische Virologie“ der GfV, Zeilitzheim

26.11.2018 Parechoviren – kaum bekannt, aber nicht irrelevant
Fortbildungsveranstaltung im Hygiene-Institut des Klinikums Nürnberg

- **Prof. Thomas Stamminger**

19.04.2017 Das humane Cytomegalovirus – von molekularen Mechanismen zu neuen Therapien
Vortrag an der Medizinischen Fakultät der Goethe-Universität, Frankfurt

22.-25.03.2017 Innate antiviral defense by PML nuclear bodies
Overview Talk, 27th Annual Meeting of the Society for Virology 2017, Marburg, Germany

17.-21.07.2017 The HCMV IE1 protein antagonizes PML nuclear body mediated intrinsic immunity via inhibition of PML de novo SUMOylation
Invited Speaker, IUMS Conference, Singapore

22.09.2017 The human CMV IE1 protein: an offender of PML nuclear bodies
Overview talk, 12th Mini-Herpesvirus Workshop, Berlin

- **Prof. Matthias Tenbusch**

02.05.2017 Gene-based immunizations against viral respiratory tract infections
Seminarvortrag, Medical Immunology Campus Erlangen

10.01.2018 Gene-based immunizations against viral respiratory tract infections
Seminarvortrag, Institut für Medizinische Virologie und Epidemiologie der Viruskrankheiten, Tübingen

16.06.2018 Gene-based immunizations against viral respiratory tract infections
Guest speaker, Annual Retreat from RTG 1949, Kamp-Lintfort

05.07.2018 Gene-based immunizations against viral respiratory tract infections
Seminarvortrag, Institut für klinische Mikrobiologie und Hygiene, Universität Regensburg

13.09.2018 Prinzip einer universellen Influenza-Vakzine
Eingeladener Sprecher beim 6. Deutschen Influenza-Kongress, Erfurt

17.12.2018 Gene-based immunizations against viral respiratory tract infections
Seminarvortrag im Rahmen des Infektionsbiologischen Seminars, Tierärztliche Hochschule Hannover

Dr. Andrea K. Thoma-Kreß

14.12.2018 Molecular insights into HTLV-1 transmission and cell-cell transport
4th IIC Christmas Symposium, DKFZ, Heidelberg

Dr. Marco Thomas

17.10.2018 A novel neutralizing epitope targeted by the anti-HCMV mAb 2B10
Institut für Virologie, Universitätsklinikum Ulm

Prof. Klaus Überla

28.04.2017 Zur Diskussion: Finanzierung von Forschung und Lehre - ein kritischer Blick und Handlungsoptionen
Professorenkonvent der Medizinischen Fakultät, Erlangen

05.10.2017 Novel approaches for HIV vaccine design and exploring efficacy
Vortrag am Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm

19.05.2018 Optimizing the HIV Env antibody response by intrastructural help
Gastvortrag an der Sektion Virologie der Medizinischen Universität Innsbruck

18.07.2018 Shingrix: eine aktuelle Risiko-Nutzen-Analyse
*27. Sitzung der Bayerischen Landesarbeitsgemeinschaft Impfen (LAGI), LGL Münche*n

14.09.2018 Labordiagnostik Influenza: von der Routine zur Pandemie
Vortrag beim 6. Deutschen Influenza-Kongress der DVV, Erfurt, 13.-15.09.2018

29.11.2018 Influenza-Pandemie: Hysterie, Wichtigtuerei oder reale Bedrohung?
Collegium Alexandrinum der Friedrich-Alexander-Universität Erlangen-Nürnberg

I. Vorlesungen und Kurse

Sommersemester 2017 bis Wintersemester 2018/19

Lectures and Courses

University Summer Term 2017 until Winter Term 2018/19

Vorlesungsverzeichnis

■ **K-V4 Vorlesung Hygiene, Mikrobiologie, Virologie**
Lecture Hygiene, Microbiology, Virology
Jedes Semester, Dozenten aktuell (WS 18/19): Prof. C. Bogdan, Prof. R. Lang, Dr. B. Kunz, Prof. K. Überla
Semesterwochenstunden: 5

■ **K-V 18 Ringvorlesung Infektiologie, Immunologie, Q4**
Practical Course Infectiology, Immunology, Q4
Jedes Semester; Dozenten aktuell (WS 18/19): Prof. R. Lang, Prof. C. Bogdan, Prof. J. Mattner, Prof. A. Ensser, Dr. K. Korn, PD Dr. F. Neipel, PD Dr. A. Knöll, Prof. T. Harrer, Prof. D. Ropers, Dr. F. Waldfahrer, Dr. S. Burghaus, PD Dr. S. Zopf, Prof. S. John, Dozenten der Universitäten Erlangen, Würzburg u. des Klinikums Nürnberg

■ **K-PS 11 - Übung Mikrobiologie, Hygiene, Immunologie u. Virologie**
Practical Course in Microbiology, Hygiene, Immunology and Virology
Jedes Semester; Dozenten aktuell (WS 18/19): Dr. G. Valenza, Dr. B. Kunz, Dr. J. Held, Prof. J. Mattner, Dr. M. Werner, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Dr. K. Korn, PD Dr. A. Knöll
Semesterwochenstunden: 3

■ **Grundlagen der Krankheitserkennung**
Principles of disease detection
Nur im WS; Dozenten aktuell (WS 18/19): Prof. A. Cavallaro, PD Dr. F. Fuchs, Prof. A. Hartmann, PD Dr. P. Hastreiter, Dr. K. Korn, Dr. B. Kunz, Prof. H. Mang, Prof. A. Pfahlberg, Prof. M. Rauh, Prof. D. S. Ropers, PD Dr. R. Strauß
Semesterwochenstunden: 4

■ **MED 45451 Experimentelle Virologie mit Demonstrationen; Wahlpflichtfach für Mediziner im 1. und 2. Studienabschnitt**
Experimental Virology with Demonstrations (compulsory optional subject for M.D. students)
Jedes Semester, Dozenten aktuell (WS 18/19): PD Dr. Biesinger-Zwosta, Prof. A. Ensser, PD Dr. A. Knöll, PD Dr. F. Neipel, Prof. M. Tenbusch, Dr. A. Thoma-Kreß
Semesterwochenstunden: 3

■ **MED 88751 Tropenmedizin einschl. Impfungen, Wahlpflichtfach im 2. Studienabschnitt**
Tropical Medicine incl. Vaccination, compulsory optional subject in the 2nd part of the course of study
Jedes Semester, Dozenten aktuell (WS 18/19): Prof. C. Bogdan, Dr. B. Kunz, Prof. S. Krappmann, Prof. R. Lang, Prof. J. Mattner, Dr. C. Schoerner, Dr. D. Wolff, Prof. T. Harrer, Prof. F. Krüger, Prof. A. Ensser, Dr. K. Korn, Dozenten der Univ. Erlangen und Würzburg u.a., Gastredner
Semesterwochenstunden: 2

■ **K-V27 Ringvorlesung Klinische Umweltmedizin / Schwerpunkt Onkologie, Q6**
Lecture Series Clinical Environmental Medicine / Focus on Oncology, Q6
Jedes Semester, Dozenten aktuell (WS 18/19): Prof. R. Fietkau, Prof. H. Drexler, PD Dr. D. Schmidt, Prof. R. Croner, Prof. L. Distel, Prof. E. Wenkel, Prof. S. Schmitz-Spanke, PD Dr. S. Semrau, PD Dr. A. Knöll
Semesterwochenstunden: 2

■ **Med. Mikrobiologie, Hygiene, Immunologie u. Virologie f. Studierende der Pharmazie (2. Studienjahr)**
Med. Microbiology, Hygiene and Immunology for Students of Pharmacy (2nd year of study)
Jedes Semester, Dozenten aktuell (WS 18/19): PD Dr. U. Schleicher, Prof. S. Krappmann, Dr. M. Petter, PD Dr. F. Neipel
Semesterwochenstunden: 3

■ **Vorlesung u. Demonstrationspraktikum für Mikrobiologie, Immunologie, Virologie und Hygiene für Zahnmediziner f. 1. klin. Semester**
Medical Microbiology, Immunology, Virology and Hygiene for Dentistry Students for 1st clinical semester
Jedes Semester, Dozenten aktuell (WS 18/19): Prof. S. Krappmann, Dr. B. Kunz, PD Dr. Dr. H. Reil
Semesterwochenstunden: 4

■ **Allgemeine Virologie**
General Virology
Jedes Semester; Dozenten im SS: Prof. B. Fleckenstein, Prof. M. Tenbusch; Dozent im WS: Prof. U. Schubert
Semesterwochenstunden: 2

■ **Spezielle Virologie**
Specialized Virology
Teil 1 – Schwerpunkt Herpesviren / **Part 1: Focus Herpesviruses**
Dozenten: PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. M. Marschall, PD Dr. M. Milbradt, PD Dr. F. Neipel
Teil 2: Schwerpunkt HIV / **Part 2: Focus HIV**
Dozenten: Prof. K. Überla, Prof. T. Gramberg, Dr. K. Korn, Prof. U. Schubert, Prof. M. Tenbusch, Dr. A. Thoma-Kreß
Teil 3: Targets, Wirkstoffe und Mechanismen der antiviralen Therapie / **Part 3: Targets, agents and mechanisms of antiviral therapy**
Dozent: Prof. M. Marschall

■ **Methods in Molecular Virology**
Jedes Semester; Dozenten aktuell (WS 18/19): Prof. K. Überla, Prof. U. Schubert, Prof. M. Tenbusch
Semesterwochenstunden: 2

■ **Aktuelle Themen der klinischen Virologie**
Current Topics in Clinical Virology
Jedes Semester; Dozenten aktuell (WS 18/19): Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, PD Dr. A. Knöll, Dr. K. Korn, Prof. M. Marschall, PD Dr. F. Neipel, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß
Semesterwochenstunden: 2

■ **Advances in Molecular Virology - Seminar mit Gastsprechern**
Seminar with Guest Speakers
Jedes Semester; Dozenten aktuell (WS 18/19): Prof. K Überla, Prof. U. Schubert, Prof. M. Tenbusch
Semesterwochenstunden: 2

■ **Einführung in das Praktikum für Mediziner**
Introduction to the Practical Course in Virology for M.D. Students
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, PD Dr. A. Knöll, Dr. K. Korn, Prof. M. Marschall, PD Dr. F. Neipel, Prof. U. Schubert, Prof. M. Tenbusch, Dr. A. Thoma-Kreß

■ **Virologisches Praktikum für Mediziner**
Practical Course in Virology for M.D. Students
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, PD Dr. A. Knöll, Dr. K. Korn, Prof. M. Marschall, PD Dr. F. Neipel, Prof. U. Schubert, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, u. Mitarbeiter
Semesterwochenstunden: 13

■ **Bachelormodul Virologie für Naturwissenschaftler, Vorlesung mit Übung**
Bachelor Module Virology for Biology Students, Lecture with Practical Course
SS und WS: Dozenten siehe Lehrveranstaltungen „Allgemeine Virologie“ und „Praktikum im Rahmen des Bachelormoduls Virologie für Naturwissenschaftler“
Modulverantwortlicher: PD Dr. B. Biesinger-Zwosta

■ **Praktikum im Rahmen des Bachelormoduls Virologie für Naturwissenschaftler**
Practical Course in Virology as part of the B.Sc. Module Virology for Students of Natural Sciences
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, PD Dr. A. Knöll, Dr. K. Korn, Prof. M. Marschall, PD Dr. J. Milbradt, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas

■ **Mastermodul Virologie für Naturwissenschaftler**
Master Module Virology for Biology Students
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas
Modulverantwortliche: PD Dr. B. Biesinger-Zwosta

■ **Vertiefungsmodul Virologie für Naturwissenschaftler**
Advanced Module Virology for Biology Students
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas
Modulverantwortliche: PD Dr. B. Biesinger-Zwosta

■ **Current Concepts in HIV Vaccine Development**
Jedes Semester; Dozenten aktuell (WS 18/19): Prof. K. Überla, PD Dr. V. Temchura, Prof. M. Tenbusch
Semesterwochenstunden: 2

■ **Molekularbiologie von Beta-Herpesviren**
Molecular Biology of Beta Herpesviruses
Jedes Semester; Dozenten aktuell (WS18/19): Prof. M. Marschall, Dr. M. Thomas
Semesterwochenstunden: 2

■ **Struktur und Funktion von HIV-Proteinen**
Structure and Function of HIV Proteins
Jedes Semester; Dozent: Prof. U. Schubert
Semesterwochenstunden: 2

■ **Vorlesung Virologie für Studenten der Molekularen Medizin (3. Fachsemester) im Rahmen des Bachelormoduls Mikrobiologie, Immunologie und Virologie**
Virology for Students of Molecular Medicine (3rd semester) as part of the B. Sc. Module Microbiology, Immunology and Virology
Nur im WS; Dozenten aktuell (WS 18/19): Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, PD Dr. A. Knöll, Prof. M. Marschall, PD Dr. F. Neipel, Prof. M. Tenbusch, Dr. A. Thoma-Kreß
Modulverantwortliche: PD Dr. B. Biesinger-Zwosta
Semesterwochenstunden: 3

■ **Einführung in das Wahlpflicht-Praxismodul F1 Virologie für Molekularmediziner**
Introduction to the Elective Practical Module F1 in Virology for Students of Molecular Medicine
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas

■ **Wahlpflicht-Praxismodul F1 Virologie für Molekularmediziner (= F1-Praktikum)**
Elective Practical Module F1 in Virology for Students of Molecular Medicine
Dozenten: Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, PD Dr. A. Knöll, Dr. K. Korn, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas

■ **Offenes Wahlpflichtmodul „Medizinische Grundlagen“ für Studenten der Molekularen Medizin**
Open Elective Module “Basic Principles of Medicine” for Students of Molecular Medicine
Angeboten von allen Dozenten des Virologischen Instituts; Kontakt: PD Dr. B. Biesinger-Zwosta

■ **Vorlesung Virologie mit Übung im Rahmen des Masterstudiengangs Molekulare Medizin: Essential Concepts in Modern Virology**
Virology – Lecture and Exercises for M.Sc. Students of Molecular Medicine: Essential Concepts in Modern Virology
Nur im SS; Dozenten (SS 2018): Prof. K. Überla, PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. M. Marschall, PD Dr. F. Neipel, PD Dr. V. Temchura
Semesterwochenstunden: 2

■ **Elective Module „Special Virology“ for M.Sc. Students of Molecular Medicine (part of Area 2 or Area 3)**
Includes an individual selection of the lectures/seminars announced under “Spezielle Virologie”
Dozenten aktuell (WS 18/19): PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas, Prof. K. Überla
Kontakt: Prof. M. Marschall

■ **Research Training in Virology for M.Sc. Students of Molecular Medicine (Area 3)**
Laboratory training course
Dozenten aktuell (WS 18/19): PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas, Prof. K. Überla
Kontakt: Prof. M. Marschall

■ **Project Development in Virology for M.Sc. Students of Molecular Medicine**
Laboratory training and project proposal
Dozenten aktuell (WS 18/19): PD Dr. B. Biesinger-Zwosta, Prof. A. Ensser, Prof. T. Gramberg, Prof. M. Marschall, PD Dr. F. Neipel, Dr. N. Reuter, Prof. U. Schubert, PD Dr. V. Temchura, Prof. M. Tenbusch, Dr. A. Thoma-Kreß, Dr. M. Thomas, Prof. K. Überla
Kontakt: Prof. M. Marschall

Alle Vorlesungen der Friedrich-Alexander-Universität
All lectures of the Friedrich-Alexander University:
http://www.univis.uni-erlangen.de

J. Seminare und Vorträge
Seminars and Workshops

Seminare mit Gastsprechern

Seminars with Guest Speakers

Datum - Date Sprecher/Thema - Speaker/Topic

2017

13.01.2017 **Dr. Krystelle Nganou Makamdop**
Vaccine Research Center, National Institutes of Health
Bethesda, MD, USA
Immune correlates of HIV acquisition

25.01.2017 *Gastseminar im Rahmen des IZKF Visiting Professor Programme*
Prof. Sylvie Le Gall
Ragon Institute of MGH, MIT and Harvard
Cambridge, MA, USA
Antigen processing and presentation in HIV infection

27.01.2017 **Prof. Päivi Ojala**
Division of Infectious Diseases, Imperial College London, UK
Kaposi's sarcoma herpesvirus as a valuable model system for cancer biology research

10.02.2017 **Prof. Robert Kalejta**
Institute for Molecular Virology, Mc Ardle Laboratory for Cancer Research, University of Wisconsin, Madison,WI, USA
Human cytomegalovirus inactivates the retinoblastoma family of tumor suppressors

23.03.2017 **Dr. David Dulin**
Interdisciplinary Center for Clinical Research (IZKF) and Optical Imaging Centre Erlangen (OICE),
Friedrich-Alexander-Universität Erlangen-Nürnberg
Biophysical studies of RNA virus replication

07.04.2017 **Prof. Paul Lieberman**
Wistar Institute, Philadelphia, PA, USA
Epigenetic control of gammaherpesvirus latency

24.04.2017 **Prof. Heiko Adler**
Helmholtz-Zentrum, München
Nanoparticles and persistent herpesvirus infection - a dangerous liaison for the development of chronic lung disease?

02.05.2017 *Immunologisches Kolloquium des Medical Immunology Campus Erlangen*
Prof. Matthias Tenbusch
Klinische und Molekulare Virologie, Universitätsklinikum Erlangen
Gene-based vaccines against respiratory tract infections

05.05.2017 **Dr. Andrea Cimarelli**
CIRI Centre International de Recherche en infectiologie, INSERM, Université de Lyon, France
Interferon-stimulated transmembrane proteins (IFITMs) as a novel paradigm of restriction factors targeting the in and out of a viral life cycle

12.05.2017 **Dr. Michael Mühlebach**
Paul-Ehrlich-Institut, Langen
Recombinant measles virus is a powerful tool in virology and biomedicine

19.05.2017 **Dr. Hongxing Zhao**
Department of Immunology, Genetics and Pathology
Uppsala University, Sweden
Multipe layers of reprogramming of host gene expression by adenovirus

02.06.2017 **Prof. Matthias Epple**
Institut für Anorganische Chemie, Universität Duisburg-Essen
Inorganic nanoparticles for drug and gene discovery

09.06.2017 **Prof. Richard Gibbons**
The Weatherall Institute of Molecular Science
University of Oxford, UK
Understanding the many roles of the chromatin remodelling factor ATRX2

23.06.2017 **Dr. Jan Eickhoff**
Lead Discovery Center GmbH, Dortmund
Pioneering translational drug discovery in Germany: From basic science to therapeutic applications

30.06.2017 **Dr. J.-M. Peloponese**
Institut de Recherche en Infectiologie de Montpellier, CNRS
Montpellier, France
HTLV-1 basic zip factor promotes leukemic transformation through alteration of protein translation

17.07.2017 **Georg F. Bischof**
University of Miami Miller School of Medicine
Miami, FL, USA
Use and limitations of recombinant rhesus monkey rhadinovirus

21.07.2017 **Prof. Ingo Drexler**
Molekulare Virologie, Universitätsklinikum Düsseldorf
Cross-competition shapes the local repertoire of tissue-resident memory CD8+ T cells

24.07.2017 **Prof. Pinghui Feng**
University of Southern California, Los Angeles, CA, USA
Herpesviruses evade nucleic acid-sensing pathways via protein deamidation

04.10.2017 **Prof. Ronald C. Desrosiers**
University of Miami Miller School of Medicine
Miami, FL, USA
The understudied sugar coating: O-linked carbohydrate on HIV and HIV gp120

20.10.2017 **Dr. Kathrin Sutter**
Virologie, Universitätsklinikum Essen
Individual antiviral and immunomodulatory properties of IFNalpha subtypes during retroviral infections

27.10.2017 **Dr. Lüder Wiebusch**
Klinik für Pädiatrie mit SP Onkologie und Hämatologie
Charité Universitätsmedizin, Berlin
Cross-regulation of cyclin A and beta-herpesviral kinases via a composite NLX-RXL element

03.11.2017 **Dr. Rayk Behrendt**
Institut für Immunologie, TU Dresden
The innate immune response to endogenous nucleic acids in infection: autoimmunity and cancer

10.11.2017 **Prof. Florian Stengel**
Department of Biology, University of Konstanz
Probing protein dynamics by chemical cross-linking and mass spectrometry

17.11.2017 **Dr. Clarissa Villinger**
Virologisches Institut, Universitätsklinikum Ulm
Characterization of HCMV morphogenesis and egress with advanced (3D) electron microscopy techniques

24.11.2017 **Prof. Bernhard Horsthemke**
Institut für Humangenetik, Universitätsklinikum Essen
Whole genome bisulfite sequencing in human monocytes and macrophages: The role of allele-specific and celltype-specific DNA methylation

08.12.2017 **Dr. Jörg Votteler**
University of Utah School of Medicine
Salt Lake City, UT, USA
Design of virus-like nanocarriers

11.12.2017 **Dr. Stuart Hamilton**
Serology and Virology Division, Prince of Wales Hospital
University of NSW, Sydney, Australia
Placental models for the prevention and treatment of congenital CMV

15.12.2017 **Prof. Dunja Bruder**
Helmholtz-Zentrum für Infektionsforschung, Braunschweig
Immune regulation in the lung in the context of respiratory tract infection

2018

26.01.2018 **Prof. Florian Klein**
Institut für Virologie, Uniklinik Köln
Evaluating antibody-mediated therapy approaches in HIV-1 infection

02.02.2018 **Prof. Paul Griffiths**
Institute of Immunology and Transplantation
University College London, UK
Quantitative studies of human cytomegalovirus in a human challenge model

19.03.2018 **Prof. Bryan R. Cullen**
Department of Molecular Genetics and Microbiology, Duke University
Durham, NC, USA
Viral epitranscriptomics

09.04.2018 **Prof. Elke Bogner**
Institut für Virologie, Charité-Universitätsmedizin Berlin
Small molecules - new CMV entry inhibitors

13.04.2018 **Prof. Bernd Lepenies**
Arbeitsgruppe Immunologie, Research Center for Emerging Infections and Zoonoses (RIZ), Stiftung Tierärztliche Hochschule Hannover
The role of myeloid C-type lectin receptors in infection and inflammation

27.04.2018 **Prof. Ravi Gupta**
Division of Infection and Immunity, University College London, UK
Cell cycle regulation and SAMHD1 activity

15.05.2018 *Immunologisches Kolloquium des Medical Immunology Campus Erlangen*
Prof. Wolfgang Kastenmüller
Institute of Experimental Immunology (IEI), University of Würzburg
Concepts of T cell activation from a spatiotemporal perspective

18.05.2018 **Prof. Christian Sinzger**
Institut für Virologie, Universitätsklinikum Ulm
Development of entry inhibitors as a strategy for treatment of human cytomegalovirus infections

25.05.2018 **Prof. Sabine Werner**
Institute of Molecular Health Sciences, ETH Zürich, Switzerland
Keratinocyte-immune cell cross-talk in skin inflammation and cancer

08.06.2018 **Prof. Xavier Saelens**
VIB-U Gent Center for Medical Biotechnology, Gent, Belgium
Prevention and treatment options for human Respiratory Syncytial Virus: small things considered

15.06.2018 **Dr. Barbara Klupp**
Friedrich-Loeffler-Institut for Tiergesundheit, Greifswald-Insel Riems
Viruses as pioneers in cell biology - molecular basis of an unusual vesicular nucleo-cytoplasmic transport

20.06.2018 **PD Dr. Sebastian Voigt**
Klinik für Pädiatrie mit Schwerpunkt Onkologie und Hämatologie, Charité-Universitätsmedizin Berlin
Virusinfektionen bei Stammzelltransplantation - das Cytomegalovirus im Fokus

22.06.2018 **Prof. Ronit Sarid**
The Mina and Everard Goodman Faculty of Life Sciences,
Bar-Ilan University, Ramat-Gan, Israel
Insights into the biology of KSHV

06.07.2018 **Prof. Chung-Pei Lee**
National Taipei University of Nursing and Health Sciences, Taiwan
Regulation of cellular environment by lytic gene products of Epstein-Barr virus

15.10.2018 **Dr. Ying Kai Chan**
Department of Genetics, Harvard Medical School, Wyss Institute for Biologically Inspired Engineering, Harvard University
Boston, MA, USA
Engineering the innate immune response to viruses

26.10.2018 **Prof. Tihana Lenac Rovis**
Center for Proteomics, Faculty of Medicine
University of Rijeka, Croatia
Mechanisms of CMV immunoevasion seen from both scientific and translational-technological perspectives

09.11.2018 **Prof. Florence Margottin**
Institut Cochin, Paris, France
HUSH antagonism by lentiviral proteins: what does it tell us about HIV latency?

23.11.2018 **Prof. Esther Schnettler**
Molecular Entomology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg
Arbovirus-mosquito interaction

30.11.2018 **Prof. Tom Broker**
Department of Biochemistry and Molecular Genetics
University of Alabama at Birmingham, AL, USA
Pathway-specific inhibitors of HPV infections - The Essential Therapeutic Safety Net

07.12.2018 **Prof. Michael Schindler**
Institut für Medizinische Virologie und Epidemiologie der Viruskrankheiten, Universitätsklinikum Tübingen
Viral immune evasion - molecular mechanisms and novel therapeutic approaches

Vortragsreihe: Methoden der Molekularen Virologie

Seminars on: Methods in Molecular Virology

Datum-Date	Sprecher/Thema-Speaker/Topic
	2017
09.01.2017	**Adriana Svrlanska** Elucidating the role of polycomb repressive complex 2 in HCMV infection
16.01.2017	**Han Xiao** Cellular factors regulating the Rev-dependent and Rev-independent expression of HIV-1 structural genes
23.01.2017	**Dr. Marco Thomas** Antibodies against cytomegaloviruses: Old questions - new team
30.01.2017	**Julia Kölle** Variability in the metabolism of the HIV-1 Gag protein
06.02.2017	**Eric Sonntag** The regulatory impact of protein kinase interaction and phosphorylation of the major cytomegaloviral core nuclear egress protein pUL50
08.05.2017	**Mirjam Steingruber, Salvador Vasquez** (Pathologisches Institut) Host interaction of HCMV protein kinase pUL97 in human cells and zebrafish
15.05.2017	**Sebastian Millen** Tax-induced signaling and a putative positive feedback loop in viral oncogenesis
22.05.2017	**Janina Deutschmann** The role of SAMHD1 in blocking endogenous and exogenous viral threats
29.05.2017	**Melanie Friedrich** The role of deubiquinating enzymes in HIV-1 replication
12.06.2017	**Rebecca Heß**, Abteilung Virologie, Ruhr-Universität Bochum Beeinflussung der antiviralen Antikörperproduktion durch differentielle Stimulation der angeborenen Immunantwort mit viralen Oberflächenproteinen
19.06.2017	**Anne-Charlotte Stilp** Inducible vector systems for elucidating the role of SPOC1 during HCMV infection
26.06.2017	**Natascha Teufert** Enhancing T cell based immunotherapy against cytomegaloviruses

03.07.2017 **Dr. Marco Thomas**
How to make HCMV gB fusogenic?

16.10.2017 **PD Dr. Frank Neipel**
Regulation of EphA2 expression by KSHV

23.10.2017 **Dominik Damm**
Particulate HIV vaccine candidates for the induction of neutralizing antibodies to HIV-1 Env in a humanized mouse model

06.11.2017 **Dr. Dennis Lapuente**
Heterologous prime-boost vaccinations against viral respiratory infections

20.11.2017 **Prof. Armin Ensser**
Opportunities of genome-wide CRISPR/CAS9 systems

27.11.2017 **Bianca Volkmann**
TRIM5alpha blocks the replication of LINE-1 retroelements

04.12.2017 **Dr. Myriam Scherer**
Entrapment of herpesviral genomes in PML nuclear bodies - a potential restriction mechanism?

18.12.2017 **Dr. Marco Thomas**
Target identification of monoclonal anti-HCMV antibodies

2018

08.01.2018 **Adrian Schmalen**
Molecular constraints that regulate strain-specific susceptibility of the HIV-1 p6 protein to IDE-mediated degradation

22.01.2018 **Pierre Tannig**
Checkpoint inhibitors as adjuvants for viral vaccines

29.01.2018 **Theresa Frank**
Functional characterization of the HCMV encoded pUS27

05.02.2018 **Melanie Friedrich**
The HIV-1 p6 Gag protein regulates ubiquitinylation of Gag that is counteracted by deubiquitinating enzymes

16.04.2018 **Dr. Vladimir Temchura**
New *in vitro* method for generation of T follicular helper cells

30.04.2018 **Prof. Walter Doerfler**
Epigenetic re-programming of the host genome upon foreign (viral) DNA invasion into cells

07.05.2018 **Stephanie Walter**
The role of DUX4 in herpesviral infection

14.05.2018 **Alexandra Herrmann**
The role of SAMHD1 in restriction and immune sensing of retroviruses and retroelements

28.05.2018 **Anna Reichel**
Role of the chromatin remodeling factor SPOC1 for human cytomegalovirus replication

04.06.2018 **Dr. Sandra Müller-Schmucker**
Intrastructural help - Search for promising epitopes in humans

11.06.2018 **Dr. Friedrich Hahn**
Artesunate-derived multimeric analogs - potent antiherpesviral activity and a unique mode of target binding

18.06.2018 **PD Dr. Brigitte Biesinger-Zwosta**
The viral oncoprotein Tio and the role of ReIB in NF-kappaB signaling

25.06.2018 **Simona Rist**
Membrane interaction of the HIV-1 p6 Gag protein

02.07.2018 **Hassan Elsayed**
Harnessing T helper cell responses induced by lincensed vaccines for improving virus-like particle based vaccination against HIV

22.10.2018 **Jana Fuchs**
Gene-based heterologous prime-boost immunizations against viral respiratory tract infections

29.10.2018 **Marius Münzberger**
EphA2-mediated signal transduction and KSHV entry

12.11.2018 **Pierre Tannig**
Coupling of HIV-1 envelope proteins onto liposomes via coiled-coil mediated heterodimerization

19.11.2018 **Dr. Melanie Friedrich**
The role of the insulin-degrading enzyme in the generation of MHC-I epitopes derived from the HIV-1 p6 Gag protein

26.11.2018 **Sebastian Millen**
Impact of the HTLV-1 induced extracellular matrix proteins COL4A1 and COL4A2 on virus processing and release

03.12.2018 **Ece Egilmezer, Dr. Stuart Hamilton (Sydney), Prof. Manfred Marschall**
CMV meets regulatory host kinases: seen from the viewpoints of Sydney Harbor bridge and Erlangen Berg

10.12.2018 **Han Xiao**
Identification of cellular factors that repress HIV-1 structural gene expression in the absence of REV

17.12.2018 **Dr. Krystelle Nganou Makamdop**
Molecular approaches for improved detection of antigen-specific responses

Vortragsreihe: Aktuelle Themen der Klinischen Virologie

Seminars on: Current Topics in Clinical Virology

Datum-Date	Sprecher/Thema-Speaker/Topic
	2017
18.01.2017	**Prof. Armin Ensser** Zika- und Chikungunyavirus - Update und aktuelle epidemiologische Entwicklungen
08.02.2017	**Dr. Andrea Thoma-Kreß** Neues zu "kick and kill" bei retroviralen Infektionen
26.04.2017	**Prof. Thomas Stamminger** Aktuelles zur Therapie von Cytomegalovirus-Infektionen
03.05.2017	**PD Dr. Antje Knöll** Aktuelles zur klinischen Relevanz der humanen Polyomaviren
10.05.2017	**PD Dr. Frank Neipel** Impfung gegen Dengue-Virus – Pro und Kontra
17.05.2017	**Prof. Ulrich Schubert** Virporine - Membranstörung bis Ionenkanal, ein update
24.05.2017	**Prof. Matthias Tenbusch** Grippeschutzimpfung: Wer, wie, was - wieso, weshalb, warum? Wer nicht impft, ist dumm??
31.05.2017	**Prof. Armin Ensser** Virale Arthritis - Übersicht und Aktuelles zur Epidemiologie
07.06.2017	**Dr. Klaus Korn** Hepatitis B: aktuelle Aspekte zur Diagnostik, Therapie und Prophylaxe
14.06.2017	**Prof. Thomas Gramberg** HERV - Der Feind in meinem Genom?
28.06.2017	**Prof. Klaus Überla** Autoimmunität und Impfung
05.07.2017	**Dr. Andrea Thoma-Kreß** Cannabis-Produkte bei viralen Infektionen
12.07.2017	**Prof. Manfred Marschall** Das endogene humane Herpesvirus iciHHV und seine klinische Relevanz

19.07.2017 **PD Brigitte Biesinger-Zwosta**
Immunpathogenese humaner Coronavirus-Infektionen

26.07.2017 **Dr. Philipp Steininger**
Infektionen und Impfung bei Patienten mit rheumatischen Erkrankungen

18.10.2017 **Dr. Klaus Korn**
Nichts ist unmöglich Teil 4 - Infektionsrisiken bei Organtransplantation

25.10.2017 **Prof. Armin Ensser**
Überblick: Zoonosen durch Negativstrang-RNA-Viren

15.11.2017 **Prof. Thomas Stamminger**
HCV-Therapie mit DAA

29.11.2017 **PD Dr. Antje Knöll**
HIV in Deutschland - aktuelle Ergebnisse aus der molekularen und epidemiologischen Forschung des RKI

06.12.2017 **Prof. Bernhard Fleckenstein**
EndPolioNow

13.12.2017 **Prof. Thomas Gramberg**
HIV und ART - Replikation im Reservoir?

20.12.2017 **Prof. Manfred Marschall**
Die Frage des Verbleibs von Influenzaviren über längere Zeiträume und intersaisonale Perioden

2018

10.01.2018 **Prof. Ulrich Schubert**
Deubiquitinylierende Enzyme - neue pharmakologische Targets für Krebs, Entzündung und Infektion

17.01.2018 **Prof. Klaus Überla**
Offene Fragen zu HPV-Impfprogrammen

07.02.2018 **Prof. Matthias Tenbusch**
Autismus durch Impfung: Die unendliche Geschichte?

18.04.2018 **PD Dr. Jens Milbradt**
Aktuelle Daten zur Influenzasaison 2017/2018

25.04.2018 **Prof. Manfred Marschall**
Molekulare Mechanismen der Pathogenese des Varizella-Zoster-Virus

02.05.2018 **Dr. Philipp Steininger**
Management von Virusinfektionen nach allogener Stammzelltransplantation

09.05.2018 **PD Dr. Brigitte Biesinger-Zwosta**
Bakteriophagen: Prävalenz, Diversität und klinisches Potential

16.05.2018 **PD Dr. Antje Knöll**
HIV-Testung

23.05.2018 **Dr. Vladimir Temchura**
Viral pathogens in freshwater: current research aspects

30.05.2018 **PD Dr. Frank Neipel**
Therapeutische Impfung gegen Hepatitis B

06.06.2018 **Prof. Ulrich Schubert**
UPS-unabhängige Generierung von MHC-1-Liganden

13.06.2018 **Prof. Matthias Tenbusch**
Respiratorische Virusinfektionen bei chronischen Lungenerkrankungen

04.07.2018 **Prof. Thomas Gramberg**
USUV - ein Emerging Flavivirus in Europa

11.07.2018 **Dr. Klaus Korn**
Interessante und überraschende Fälle aus der virologischen Diagnostik

17.10.2018 **Dr. Philipp Steininger**
Therapie von Patienten mit HIV-Infektion im klinischen Alltag

24.10.2018 **Dr. Klaus Korn**
Parechoviren - wenig bekannt, aber durchaus relevant

31.10.2018 **Prof. Klaus Überla**
Prävention nosokomialer Influenzavirus-Infektionen

14.11.2018 **PD Dr. Antje Knöll**
Tollwut

21.11.2018 **Prof. Ulrich Schubert**
Viroporine - ein Update

12.12.2018 **Prof. Armin Ensser**
ZNS-Erkrankungen durch Bornaviren

19.12.2018 **Prof. Thomas Gramberg**
West-Nil-Virus in Deutschland 2018

Vorträge im Rahmen von Promotionsprüfungen

Oral Presentations for Doctoral Examinations

Datum-Date **Sprecher/Thema-Speaker/Topic**

2017

10.01.2017 **Christine Groß, M.Sc.**
Effects of the viral Tax protein on cell-to-cell transmission of Human T-cell leukemia virus type 1 (HTLV-1)

20.06.2017 **Benjamin von Bredow, M.Sc.**
Exchange student of the GRK/ Resesarch Training Program 1071; Mentor: Prof. D. Evans, Madison
Mechanisms of resistance to antibody-dependent cell-mediated cytotoxicity by HIV

11.07.2017 **Eva-Maria Schilling, M.Sc.**
Funktionsmechanismus der de-SUMOylierung durch das Regulatorprotein IE1 des humanen Cytomegalovirus

04.10.2017 **Sebastian P. Fuchs, M.Sc.**
Exchange student of the GRK/ Resesarch Training Program 1071; Mentor: Prof. R. C. Desrosiers, Miami
AAV-mediated antibody gene transfer for the prevention and treatment of immunodeficiency virus infection in rhesus monkeys

2018

13.03.2018 **Georg F. Bischof, M.Sc.**
Exchange student of the GRK/ Resesarch Training Program 1071; Mentor: Prof. R. C. Desrosiers, Miami
Recombinant Rhesus Monkey Rhadinovirus: *In Vivo* Evaluation of a Herpesviral Gene Transfer and Vaccine Vector System

08.05.2018 **Eric Sonntag, M.Sc.**
Mechanisms of Formation and Function of the Human Cytomegalovirus-Specific Nuclear Egress Complex

25.06.2018 **Anna Reichel, M.Sc.**
Role of the chromatin remodeling factor SPOC1 for human cytomegalovirus replication

17.07.2018 **Theresa Frank, M.Sc.**
Analysis of signaling and immunomodulatory functions of the HCMV encoded viral G protein-coupled receptors pUS27 and pUS28

18.07.2018 **Melanie Friedrich, M.Sc.**
Die Rolle des Ubiquitin-Proteasom-Systems in den späten Prozessen der HIV-1 Replikation

31.07.2018 **Alexandra Herrmann, M.Sc.**
The role of SAMHD1 in restriction and immune sensing of retroviruses and retroelements

20.11.2018 **Hassan Elsayed, M.Sc.**
Harnessing T helper cell responses induced by licensed vaccines for improving virus-like particle based vaccination against HIV

Ärztliche Fortbildungsveranstaltungen

Die Fortbildungsreihe besteht seit 1995. Seit Anfang 1999 wird diese Serie von Fortbildungsveranstaltungen über aktuelle Themen aus der Epidemiologie, Diagnostik, Therapie und Prophylaxe von Infektionskrankheiten nun gemeinsam mit dem Mikrobiologischen Institut - Klinische Mikrobiologie, Immunologie und Hygiene organisiert. Die Fortbildungsveranstaltungen für Ärztinnen/Ärzte (und auch alle anderen Interessierten) finden alle zwei Monate im Hörsaal des Mikrobiologischen Instituts, Wasserturmstraße 3-5, statt. Programmankündigungen mit Zusammenfassungen der Vorträge werden nach Anforderung ca. drei Wochen vor der Veranstaltung zugeschickt. Die Ankündigung der aktuellen Veranstaltung sowie Links zu den Themen und Abstracts früherer Veranstaltungen finden Sie darüber hinaus auch auf der Homepage des Instituts.

Continuing Medical Education

The seminar program for continuing medical education exists since 1995. Since the beginning of 1999 this series of evening seminars on current topics in epidemiology, diagnosis, treatment and prophylaxis of infectious diseases is organized together with the Department for Clinical Microbiology, Immunology and Hygiene of the University of Erlangen-Nuremberg. These seminars for physicians (and all other interested persons) are held every two months in the lecture hall of the Institute of Microbiology, Wasserturmstraße 3-5. Announcements (in German) are sent out on request about 3 weeks before the event. The announcement of the forthcoming seminar as well as links to the announcements and/or abstracts of previous seminars can also be found on the homepage of the institute (all in German).

Ansprechpartner/*Contact: Dr. Klaus Korn*
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E-mail:
klaus.korn@uk-erlangen.de

25. Januar 2017
Impfungen

- **Fallvorstellung 1**
  Dr. med. Barbara Jüngert
  Institut und Poliklinik für Arbeits-, Sozial- und Umweltmedizin, Friedrich-Alexander-Universität Erlangen-Nürnberg

- **STIKO-Update 2017 und Darstellung der Pneumokokken-Impfempfehlung für Senioren**
  Prof. Dr. med. Christian Bogdan
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Fallvorstellung 2**
  Markus Werner
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Impfungen gegen Varizella-Zoster-Virus**
  PD Dr. med. Frank Neipel
  Virologisches Institut, Universitätsklinikum Erlangen

29. März 2017
Infektionen der Haut und der Hautanhangsgebilde

- **Fallvorstellung 1**
  Judith Popp, Assistenzärztin
  Hautklinik, Universitätsklinikum Erlangen

- **Fallvorstellung 2**
  Dr. med. Olga Böhm, Assistenzärztin
  Hautklinik, Universitätsklinikum Erlangen

- **Pilzinfektionen der Haut und der Hautanhangsgebilde**
  Dr. med. Dorit Wolff
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Hautinfektionen durch Papillom- und Polyomaviren**
  Dr. med. Klaus Korn
  Virologisches Institut, Universitätsklinikum Erlangen

21. Juni 2017
Infektionen von Niere und Harnwegen

- **Fallvorstellungen**
  Wencke Losenky, Assistenzärztin
  Urologische und Kinderurologische Klinik, Universitätsklinikum Erlangen

- **Update – mikrobiologische Diagnostik und Therapie von Harnwegsinfektionen**
  Dr. med. Jürgen Held, Oberarzt
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Fallvorstellung**
  PD Dr. med. Tilman Ditting, Oberarzt
  Medizinische Klinik 4, Nephrologie und Hypertensiologie, Universitätsklinikum Erlangen/Klinikum Nürnberg

- **„Von Mäusen und Menschen" – Infektionen durch Hantaviren**
  Dr. med. Klaus Korn
  Virologisches Institut, Universitätsklinikum Erlangen

08. November 2017
Ektoparasiten: Läuse, Flöhe, Milben & Co.

- **Fallvorstellungen**
  Markus Werner
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Läuse und Flöhe - Aktuelles aus der Sicht des Gesundheitsamtes**
  Dr. med. Frank Neumann
  Leiter des Staatlichen Gesundheitsamtes Erlangen-Höchstadt

- **Klinik, Diagnostik und Therapie der Scabies**
  Prof. Dr. med. Frank Kiesewetter
  Hautklinik, Universitätsklinikum Erlangen

- **Ektoparasiten als Reisemitbringsel**
  Prof. Dr. med. Christian Bogdan
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

  Müssen wir mit neuen vektorübertragenen Virusinfektionen rechnen?
  Dr. med. Klaus Korn
  Virologisches Institut, Universitätsklinikum Erlangen

31. Januar 2018
Infektionen bei Patienten nach Transplantationen

- **Fallvorstellung 1**
  Dr. med. Lisa Meintker
  Medizinische Klinik 5, Hämatologie und Internistische Onkologie, Universitätsklinikum Erlangen

- **Neue Optionen für die CMV-Prophylaxe bei Transplantationspatienten**
  Dr. med. Philipp Steininger
  Virologisches Institut, Universitätsklinikum Erlangen

- **Fallvorstellung 2**
  Dr. med. Christian Schmidt-Lauber
  Medizinische Klinik 4 – Nephrologie und Hypertensiologie, Universitätsklinikum Erlangen

- **Epidemiologie von Candida-Infektionen am Universitätsklinikum Erlangen**
  Prof. Dr. med. Roland Lang
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Diagnostik von Infektionen nach Transplantation**
  Dr. med. Jürgen Held
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

11. April 2018
Infektionen im Alter

- **Epidemiologie von Influenza- und Norovirus-Infektionen: wie stark sind ältere Patienten betroffen?**
  Dr. med. Klaus Korn
  Virologisches Institut, Universitätsklinikum Erlangen

- **Impfprophylaxe der Influenza und des Herpes zoster**
  Prof. Dr. med. Klaus Überla
  Virologisches Institut, Universitätsklinikum Erlangen

- **Fallvorstellung 1**
  Dr. med. Julia Fürst
  Medizinische Klinik 1, Gastroenterologie, Pneumologie und Endokrinologie, Universitätsklinikum Erlangen

- **Pharmakotherapie im Alter**
  Dr. rer. nat. Sonja Koch
  Apotheke, Universitätsklinikum Erlangen

- **Fallvorstellung 2**
  Dr. med. Stefan Jungbauer
  Medizinische Klinik 1 – Gastroenterologie, Pneumologie und Endokrinologie, Universitätsklinikum Erlangen

- **Infektionen und Immunabwehr im Alter**
  Prof. Dr. med. Jochen Mattner
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

27. Juni 2018
Infektionen im HNO-Bereich

- **Fallvorstellung 1**
  Dr. med. Andreas Reichelt
  Hals-Nasen-Ohren-Klinik – Kopf- und Halschirurgie, Universitätsklinikum Erlangen

- **Fallvorstellung 2**
  Dr. med. Franziska Kißlinger, Dr. med. Robin Rupp
  Hals-Nasen-Ohren-Klinik – Kopf- und Halschirurgie, Universitätsklinikum Erlangen

- **Otitis, Tonsillitis, Sinusitis: Ätiologie, Diagnostik und Therapie**
  Anca Gavrilut
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Fallvorstellung 3**
  Dr. med. Dr. med. dent. Raimund Preidl
  Mund-, Kiefer- und Gesichtschirurgische Klinik, Universitätsklinikum Erlangen

- **Humane Papillomviren im Mund- und Rachenraum**
  PD Dr. med. Antje Knöll
  Virologisches Institut, Universitätsklinikum Erlangen

07. November 2018
Chronisches Erschöpfungssyndrom (chronic fatigue) – eine Komplikation von Infektionen?

- **Erkrankungen beim Menschen durch Bornaviren – was gibt es Neues?**
  Dr. med. Klaus Korn
  Virologisches Institut, Universitätsklinikum Erlangen

- **Herpesviren und das chronische Erschöpfungssyndrom – eine schwierige Melange**
  PD Dr. med. Frank Neipel
  Virologisches Institut, Universitätsklinikum Erlangen

- **Chronisches Erschöpfungssyndrom durch Borrelia burgdorferi – Realität oder Mythos?**
  Dr. med. Caroline Kunz
  Mikrobiologisches Institut, Universitätsklinikum Erlangen

- **Metabolische Signaturen beim chronischen Erschöpfungssyndrom**
  Dr. med. Philipp Steininger
  Virologisches Institut, Universitätsklinikum Erlangen

- **Klinik und pathophysiologische Modelle des CFS/ME**
  Prof. Dr. med. Thomas Harrer
  Medizinische Klinik 3, Universitätsklinikum Erlangen

K. Dissertationen, Abschlussarbeiten
Dissertations, Theses

Bachelorarbeiten

Bachelor Theses

Disch, Alina, Biologie, Abschluss: 05/2018
Identifikation eines von der Regulation durch das KSHV Replikations- und Transkriptionsaktivator-Protein (RTA) unabhängigen Promotors
Betreuer: Prof. W. Kreis, PD Dr. F. Neipel

Göttlicher, Tim, Biologie, Abschluss: 02/2017
Die Expression des viralen Tax-1 Onkoproteins in Abhängigkeit von NF-κB Signalen
Betreuer: Prof. R. Slany, Prof. B. Fleckenstein/Dr. A. Thoma-Kreß

Heym, Stefanie, Bioanalytik (FH), Abschluss: 02/2018
Untersuchungen zum Zell-Zell-Transport des viralen Proteins p8 des Humanen T-Zell-Leukämie-Virus Typ 1 (HTLV-1)
Betreuer: A. Vondran (FH Coburg), Dr. A. Thoma-Kreß

Kühnert, Franziska, Molekulare Medizin, Abschluss: 06/2017
Analysis of the HIV-induced ISG-response in SAMHD1-KO mice
Betreuer: Prof. C. Lie, Prof. T. Gramberg

Lauffer, Marius, Biologie, Abschluss: 07/2018
Die Rolle der Integrine αVβ3 und α3β1 bei der Infektion epithelialer Zellen durch das Kaposi-Sarkom-assoziierte Herpesvirus
Betreuer: Prof. W. Kreis, PD Dr. F. Neipel

Mautner, **Lena,** Molekulare Medizin, Abschluss: 08/2017
Untersuchungen zur Rolle des Cytomegalovirus-Regulatorproteins IE1 für die Induktion einer zellulären DNA-Schadensantwort
Betreuer: Prof. T. Stamminger, Prof. H. Sticht

Niesar, Aischa, Integrated Life Sciences, Abschluss: 09/2018
Analyse von antiviral und antitumoral wirksamen Kinase-Inhibitoren in Bezug auf die Spezifität für die Cytomegalovirus-Proteinkinase pUL97
Betreuer: Prof. M. Marschall/Dr. F. Hahn (Zweitberichterstatter Prof. U. Sonnewald)

Pfeil, Tobias, Bachelor Biologie
Antikörpern gegen das cytomegalovirale Glykoprotein H
Betreuer: Dr. Marco Thomas, Gutachter: Prof. Michael Mach

Reidel, Alexander, Integrated Life Sciences, Abschluss: 09/2018
Der Einfluss muriner Wirtsfaktoren auf LINE-1 Elemente
Betreuer: Prof. R. Slany, Prof. T. Gramberg

Schmidt, **Anna**, Molekulare Medizin, Abschluss: 08/2018
Etablierung von Reporterassays zur Quantifizierung von Influenza-A-Viren
Betreuer: Prof. M. Tenbusch

Schmidt, Katja, Molekulare Medizin, Abschluss 07/2018
Das Epstein-Barr-Virus-Onkoprotein LMP1 hemmt die IRF7-vermittelte Interferon-Induktion
Betreuer: PD Dr. Brigitte Biesinger-Zwosta

Schmitt, Sarah, Biologie, Abschluss: 07/2017
Steigerung der Expression des viralen Tax-1 Onkoproteins durch NF-κB Aktivität
Betreuer: Prof. R. Slany, Prof. B. Fleckenstein/Dr. A. Thoma-Kreß

Schrödel, Tobias, Biologie, Abschluss: 11/2017
Der Einfluss von CRISPR/Cas9 spezifisch induziertem Gen-Knockout auf die HIV-1-Rev abhängige und unabhängige Strukturgen-Expression
Betreuer: Prof. K. Überla, Prof. A. Burkovski

Sommer, Benedikt, Molekulare Medizin, Abschluss: 09/2018
Regulation der EphA2-Rezeptortyrosinkinase durch RTA auf post-transkriptionellem Weg
Betreuer: PD B. Biesinger-Zwosta, PD Dr. F. Neipel

Wagner, Jannik Till, Integrated Life Sciences, Abschluss: 07/2018
Analyse von positionsspezifischen Mutationen in regulatorischen Proteinen des humanen Cytomegalovirus hinsichtlich deren Interaktion mit Cyclinen
Betreuer: Prof. M. Marschall (Zweitberichterstatter Prof. A. Burkovski)

Masterarbeiten Master Theses

Aberle, Tim, Molekulare Medizin, Abschluss: 10/2018
Interaction between cyclins and cytomegalovirus protein kinase pUL97-binding domains and regulatory consequences
Betreuer: Prof. R. Slany, Prof. T. Gramberg

Bayerlein, Jasmin, Zell- und Molekularbiologie
Evaluation von cRIG-I und IPS1 als genetische Adjuvantien in adenoviralen Immunisierungen gegen Influenza A Viren
Betreuer: Prof. M. Tenbusch

Dittmar, Michael, Biologie, Abschluss: 02/2017
Identification and characterisation of neutralizing antibodies against the HHV-8 glycoproteins gH and gL
Betreuer: PD Dr. F. Neipel (Erstberichterstatter Prof. T. Winkler)

Giller, Nadine, Master Bioanalytik, Hochschule Coburg, Abschluss: 08/2017
Das cytomegalovirale Glykoprotein B – Generierung von Zelllinien mit induzierbarer gB-Expression & Produktion von gB-spezifischen Antikörpern
Betreuer: Dr. Marco Thomas, Gutachter: Prof. Dr. Matthias Noll (Hochschule Coburg)

Häge, Sigrun, Biologie, Abschluss: 04/2018
Analysis of the functional conservation of herpesviral core NEC proteins
Betreuer: Prof. M. Marschall (Zweitberichterstatter Prof. B. Kost)

Horsch, Deborah, Molekulare Medizin
Phenotypic analysis of recombinant cytomegaloviruses regarding replacement mutations in phosphorylation sites of the viral nuclear egress complex
Betreuer: Prof. M. Marschall/Dr. E. Sonntag (Zweitberichterstatter Prof. H. Sticht)

Keller, Lena, Molekulare Medizin, Abschluss: 01/2018
Characterization of the interaction between cyclin H and the viral protein kinase pUL97 during cytomegalovirus replication
Betreuer: Prof. M. Marschall (Zweitberichterstatter Prof. M. Stürzl)

Kohrt, Stephan, Biologie
Characterization of the interaction between cyclin H and the viral protein kinase pUL97 during cytomegalovirus replication
Betreuer: Prof. M. Marschall (Zweitberichterstatter Prof. M. Stürzl)

Lechner, Kristina, Molekulare Biomedizin, WWU Münster, Abschluss 05/2017
RelB-dependent gene regulation and IL13 induction via the viral oncoprotein Tio
Betreuer: PD Dr. Brigitte Biesinger-Zwosta

Matthaei, Alina, Molekulare Medizin, Abschluss: 10/2018
The role of the insulin-degrading enzyme in proteasome-independent generation of MHC-I epitopes derived from the HIV-1 p6 Gag protein
Betreuer: Prof. U. Schubert

Ogungbemi, Victoria Kehinde, Master Biomedizin und Biotechnologie, Abschluss: 09/2018
Analysis of HCMV gB Fusion Activity & Production of recombinant antibodies against gB and gN
Betreuer: Dr. Marco Thomas, Gutachter: Prof. Dr. Tillman Rümenapf (Institut für Virologie, Veterinärmedizinische Universität Wien)

Peter, Antonia Sophia, Zell- und Molekularbiologie, Abschluss: 11/2018
Etablierung eines chaotropen Aviditäts-Tests und Einfluss von Checkpoint Inhibitoren auf die durch Impfung induzierte Avidität
Betreuer: Prof. K. Überla

Rist, Simona, Zell- und Molekularbiologie, Abschluss: 08/2017
Untersuchungen zur Oligomerisierung und intrazellulären Lokalisation des p6 Gag-Proteins von HIV-1
Betreuer: Prof. U. Schubert

Ross, Julian, Molekulare Medizin, Abschluss: 04/2018
The role of murine TRIM5 orthologues in innate immune signaling and restriction of transposable elements
Betreuer: Prof. C. Lie, Prof. T. Gramberg

Schrumpf, Johannes, Molecular Science, Abschluss: 09/2017
The influence of murine TRIM5α orthologues on the replication of endogenous retroelements
Betreuer: Prof. C. Koch, Prof. T. Gramberg

Schütz, Martin, Biologie
Functional interaction between the peptidyl prolyl isomerase Pin1 and regulatory proteins of human cytomegalovirus
Betreuer: Prof. M. Marschall (Zweitberichterstatter N.N.)

Stangl, Sonja, Molecular Life Sciences, Abschluss: 06/2017
Development of a simultaneous HIV challenge model
Betreuer: Prof. K. Überla

Wolf, Lina, Zell- und Molekularbiologie, Abschluss: 10/2018
Einfluss der NF-κB Aktivität auf die Stabilität des viralen Tax-Proteins des HTLV-1
Betreuer: Prof. A. Burkovski, Prof. B. Fleckenstein/Dr. A. Thoma-Kreß

Dissertationen ■ Doctorate Theses

Böhm, Magdalena, Cand. med.
Invention of a phenotypical resistance testing for HIV-1 subtypes
Betreuer: Prof. K. Überla

Damm, Dominik, M.Sc.
Modulation of the antibody response to the HIV envelope protein
Betreuer: Prof. K. Überla

Dedden, Christoph, Cand.med.
Ruhr-Universität Bochum
Nachweis bislang nicht bekannter Viren durch Next Generation Sequencing (NGS) bei Patienten mit schwerer Immundefizienz nach allogener Stammzelltransplantation
Betreuer: Prof. K. Überla

Deutschmann, Janina, Biologie, M.Sc.
Regulation of the antiviral activity of SAMHD1
Betreuer: Prof. T. Gramberg

Elsayed, Hassan, M.Sc., Abschluss: 11/2018
Enhancement of HIV Env Specific Antibody Responses by Intrastructural Help from Heterologous T Helper Cells
Betreuer: Prof. K. Überla

Frank, Theresa, M.Sc.
Functional selectivity as a result of viral chemokine receptor heterodimerization
Betreuer: Prof. T. Stamminger, Dr. N. Tschammer

Friedrich, **Melanie**, M.Sc., Abschluss: 07/2018
Die Rolle des Ubiquitin-Proteasom-Systems in den späten Prozessen der HIV-1 Replikation
Betreuer: Prof. U. Schubert

Frank, Theresa, Molecular Sciences, M.Sc., Abschluss: 07/2018
Analysis of signaling and immunomodulatory functions of the HCMV encoded viral G protein-coupled receptors pUS27 and pUS28
Betreuer: Prof. T. Stamminger

Fuchs, **Jana**, M.Sc.
Genbasierte heterologe prime/boost-Immunisierungen gegen virale Atemwegserkrankungen
Betreuer: Prof. M. Tenbusch

Groß, Christine, Zell-und Molekularbiologie, M.Sc., Abschluss 01/2017
Effects of the viral Tax protein on cell-to-cell transmission of Human T-cell leukemia virus type 1 (HTLV-1)
Betreuer: Prof. B. Fleckenstein/Dr. A. Thoma-Kreß, Prof. A. Burkovski

Häge, Sigrun, Master Biol.
Functional analysis of herpesviral nuclear egress complexes as a putative target for novel antiviral drugs
Betreuer: Prof. M. Marschall (Zweitberichterstatter N.N.)

Herrmann, Alexandra, M.Sc., Abschluss: 07/2018
The role of SAMHD1 in restriction and immune sensing of retroviruses and retroelements
Betreuer: Prof. T. Gramberg

Heß, **Rebecca**, M.Sc., Abschluss: 07/2017
Abteilung für molekulare und medizinische Virologie, Ruhr-Universität Bochum
Differential stimulation of innate immune responses by viral surface proteins modulating the antiviral antibody response
Betreuer: Prof. K. Überla, Prof. M. Tenbusch

Karam, Louna, Biologie M.Sc., Abschluss: 06/2018
Mode of action of new therapeutic drugs in the treatment of HHV-8-associated primary effusion lymphoma
Betreuer: Prof. R. Abou-Merhi, PD Dr. F. Neipel

Klessing, Stephan, M.Sc.
Optimizing the memory B cell response by intrastructural help
Betreuer: Prof. K. Überla

König, Patrick, Biologie, M.Sc.
Virale Modulation der zellulären Proteinkinase ULK1
Betreuer: Prof. T. Stamminger

Kolenbrander, Anne, M.Sc., Abschluss: 02/2017
Abteilung für Molekulare und Medizinische Virologie, Ruhr-Universität Bochum
Characterization and modulation of HIV Env specific B cell differentiation induced by Virus-like Particle Vaccine
Betreuer: Prof. K. Überla

Lapuente, **Dennis**, M.Sc., Abschluss: 04/2017 (*summa cum laude*)
Abteilung für molekulare und medizinische Virologie, Ruhr-Universität Bochum
Evaluation of IL-1β and IL-18 as genetic adjuvants in adenoviral immunizations against influenza A viruses
Betreuer: Prof. M. Tenbusch

Maaske, **André**, M.Sc., Abschluss: 04/2017
Abteilung für molekulare und medizinische Virologie, Ruhr-Universität Bochum
Treatment of allergic asthma by gene based immunizations that induce specific targeting of antigens toward dendritic cells
Betreuer: Prof. M. Tenbusch

Maier, Clara, Cand. med.
Signalmoleküle der angeborenen Immunantwort als genetische Adjuvantien bei adenoviralen Vektorimmunisierungen gegen das Respiratorische Synzytial Virus (RSV)
Betreuer: Prof. M Tenbusch

Millen, Sebastian, Zell-und Molekularbiologie, M.Sc.
Inhibition of signal transduction during Tax-induced transmission of Human T-cell lymphotropic virus type I (HTLV-1)
Betreuer: Prof. A. Burkovski, Prof. K. Überla/Dr. A. Thoma-Kreß,

Reichel, Anna, Biologie, M.Sc., Abschluss: 06/2018
Role of the chromatin remodeling factor SPOC1 for HCMV replication
Betreuer: Prof. T. Stamminger

Richel, Elie, M.Sc.
Relevance of Fc-effector functions for prevention of the first cell in the HIV non-human primate model
Betreuer: Prof. K. Überla

Rist, Simona, M.Sc.
Die Funktion des reifen HIV-1 p6 Proteins
Betreuer: Prof. U. Schubert

Ruhland, Anna, Cand. med.
Charakterisierung der antiviralen Wirkung von Wedelolaktone auf die Cytomegalovirus-Infektion
Betreuer: Prof. T. Stamminger

Schmalen, Adrian, M.Sc.
Einfluss des HIV-1 p6 Gag Proteins auf den viralen Replikationszyklus
Betreuer: Prof. U. Schubert

Sonntag, Eric, Master Biol., Abschluss: 03/2018
Mechanisms of formation and function of the human cytomegalovirus-specific nuclear egress complex
Betreuer: Prof. M. Marschall (Zweitberichterstatter Prof. Dr. A. Burkovski)

Steingruber, Mirjam, Master Biol.
Molecular mode of interaction between the cytomegalovirus CDK ortholog pUL97 and cyclins
Betreuer: Prof. M. Marschall (Zweitberichterstatter N.N.)

Svrlanska, Adriana, M.Sc.
Modulation epigenetischer Regulationsvorgänge durch das IE2-Protein des humanen Cytomegalovirus
Betreuer: Prof. T. Stamminger

Tannig, Pierre, M.Sc.
Checkpoint inhibitors as adjuvants for viral vaccines
Betreuer: Prof. K. Überla

Teufert, Natascha, M.Sc., Abschluss: 02/2019
T-Zell-basierte Immuntherapie gegen Cytomegalovirusinfektionen – Weiterentwicklung mittels bispezifischer Antikörper
Betreuer: Prof. A. Ensser

Volkmann, Bianca, M.Sc.
Analysis of host restriction factors on the life cycle of retroviruses
Betreuer: Prof. T. Gramberg

Walter, Stephanie, M.Sc.
The role of DUX4 in herpesviral replication
Betreuer: Prof. A. Ensser

Weidl, Daniel, M.Sc.
Interferon-Suppression durch herpesvirale Onkoproteine
Betreuer: PD Dr. Brigitte Biesinger-Zwosta

Xiao, Han, M.Sc.
Identification of Cellular Factors Regulating HIV-1 Late Gene Expression
Betreuer: Prof. K. Überla

L. Mitgliedschaft in Gremien, Berufungen, Auszeichnungen Memberships in Boards, Appointments, Awards

Mitgliedschaft in akademischen Gremien

Prof. Dr. Klaus Überla

- Mitglied der Ständigen Impfkommission (STIKO) des Robert-Koch-Instituts, Vorsitzender der Arbeitsgemeinschaft Varizella-Zoster-Virus
- Mitglied der Bayerischen Landesarbeitsgemeinschaft Impfen (LAGI)
- Schatzmeister der Gesellschaft für Virologie (GfV)
- Vorsitzender des *Vereins zur Förderung der Virusforschung e.V.(*seit Juli 2015)
- Mitglied der folgenden Gremien der Medizinischen Fakultät der Universität Erlangen-Nürnberg:
  - Fakultätsrat
  - Komission für wissenschaftlichen Nachwuchs (Vorsitzender)
  - Kommission für Bauangelegenheiten
  - Kommission für Forschung (bis 2018)
  - ELAN-Ausschuss
  - Beirat der Johannes und Frieda Marohn-Stiftung
- Berichterstatter für Berufungsverfahren an der Universität Erlangen-Nürnberg
- Editorial Board *Retrovirology*
- Editorial Board *Innate Immunity*

Prof. Dr. Dr. h.c. Walter Doerfler

- Mitglied der *European Molecular Biology Organization* (EMBO)
- Mitglied der Deutschen Akademie der Naturforscher Leopoldina – Nationale Akademie der Wissenschaften
- Mitglied der Editorial Boards von *Epigenetics* und *Virus Research*
- *Board Ventnor Foundation Alumni e. V.* – Essen & Thomasville, GA, USA

Dr. Klaus Korn

- Gemeinsame Kommission für Virusdiagnostik der GfV und DVV

Prof. Dr. Manfred Marschall

- Gründungsmitglied des *Optical Imaging Center Erlangen* (OICE); Gründung 10/2011, Sprecher Prof. Vahid Sandoghdar
- Mentor im Max Weber-Programm Bayern der Studienstiftung des deutschen Volkes

Prof. Dr. Thomas Stamminger

- Editorial Board *Viruses*
- Editorial Board *Scientifica* (Research Area: Microbiology)
- Academic Editor of *British Microbiology Research Journal*
- Stellvertretender Sprecher des SFB 796 *Steuerungsmechanismen mikrobieller Effektoren in Wirtszellen* (bis 31.12.2017)
- Mitglied des externen wissenschaftlichen Gutachtergremiums der Universität Padua
- *International Advisory Committee* des *42nd Annual International Herpesvirus Workshop*, 29.07.-02.08.2017, Ghent, Belgium
- *International Advisory Committee* der IUMS 2017 Singapore Conference, 17.07.-21.07.2017, Singapur

Prof. Dr. Matthias Tenbusch

- Mitglied der Kommission “Immunisierung” der GfV und DVV

Berufungen

■ Prof. Dr. Thomas Stamminger

11/2016 Ruf auf den Lehrstuhl für Virologie der Universität Wien (Österreich) (Rufabsage 10/2017)

05/2017 Ruf auf den Lehrstuhl für Virologie der Universität Ulm (Rufannahme 11/2017)

■ Prof. Dr. Matthias Tenbusch

01.02.2017 Antritt der W2-Professur für Genbasierte Immunisierungsverfahren am Virologischen Institut - Klinische und Molekulare Virologie

Habilitationen

■ PD Dr. (Univ. Nowosibirsk) Dr. habil. med. Vladimir Temchura

11/2018 Verleihung des akademischen Grads eines habilitierten Doktors der Medizin und Anerkennung der Lehrbefähigung durch die Friedrich-Alexander-Universität Erlangen-Nürnberg im Fachgebiet Virologie der Medizinischen Fakultät; Titel der Habilitationsschrift: *Nanoparticle-based antiviral vaccines: from rational design to preclinical evaluation*

28.11.2018 Öffentliche Antrittsvorlesung am Virologischen Institut zum Thema *Antiviral vaccines: from empirical past to rationally designed future*

02/2019 Erteilung der Lehrbefugnis durch die Friedrich-Alexander-Universität Erlangen-Nürnberg im Fachgebiet Virologie der Medizinischen Fakultät

Auszeichnungen

Prof. Dr. Dr. h.c. Walter Doerfler

26.01.2018 Verleihung der Ehrendoktorwürde der Medizinischen Fakultät der Universität Uppsala, Schweden (Dr. med. h.c. – Hedersdoktor)

09./10.03.2018 60th Anniversary, Department of Biochemistry, Stanford University

11.07.2018 Gutachter für die Ausschreibung „EPIGENETIK“ der Baden-Württemberg-Stiftung in Stuttgart; durchgeführt durch Molekulare Lebenswissenschaften Forschungszentrum Jülich GmbH

17.07.2018 Invitation for Review in EPIGENETICS by Dr. Manel Esteller (Editor in Chief): Doerfler, W., Weber, S., Naumann, A. (2018). Inheritable epigenetic response towards foreign DNA entry by mammalian host cells: a guardian of genomic stability. doi: 10.1080/15592294.2018.1549463. Epigenetics 13, 1141–1153

06.-08.10.2018 34th Ernst-Klenk-Symposium, Universität zu Köln, “*Epigenetics: Basic principles and clinical applications”*, Co-organizer, Session Chair

Prof. Dr. Thomas Gramberg

06.11.2017 Verleihung des Thiersch-Preises der Medizinischen Fakultät der Universität Erlangen-Nürnberg für die beste Habilitationschrift des Jahres 2016; Titel: *Die Rolle von SAMHD1 als Restriktionsfaktor der retroviralen Infektion*

Alexandra Herrmann (AG Gramberg)

18.12.2018 Reisestipendium des Vereins zur Förderung der Virusforschung e.V. für den besten Doktorandenvortrag 2018 in der Seminarreihe *„Methods in Molecular Virology“*

Dr. Dennis Lapuente (AG Tenbusch)

15/16.05.2017 Promotionspreis *„Scientific Excellence Award”* des RTG1949 “Immune Response in Infectious Diseases – Regulation between Innate and Adaptive Immunity” Annual Retreat

Dr. Andrea Thoma-Kreß

07/2017 *Exploration Grant* der Boehringer Ingelheim-Stiftung

■ Adriana Svrlanska (AG Stamminger)

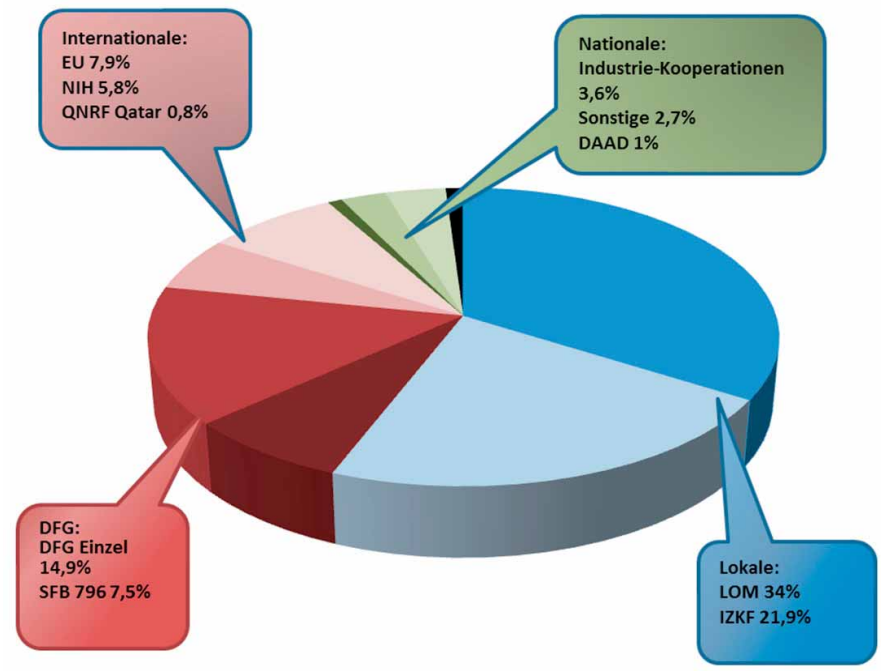
07/2017 Priscilla Schaffer Award, 42st Annual International Herpesvirus Workshop, 29.07.-02.08.2017, Ghent, Belgium

■ Daniel Weidl (AG Biesinger)

09.04.2018 Reisestipendium des Vereins zur Förderung der Virusforschung e.V. für den besten Doktorandenvortrag des Wintersemesters 2017/2018 in der Seminarreihe *„Methods in Molecular Virology“*

M. Finanzielle Förderung des Instituts
Financial Support of the Institute

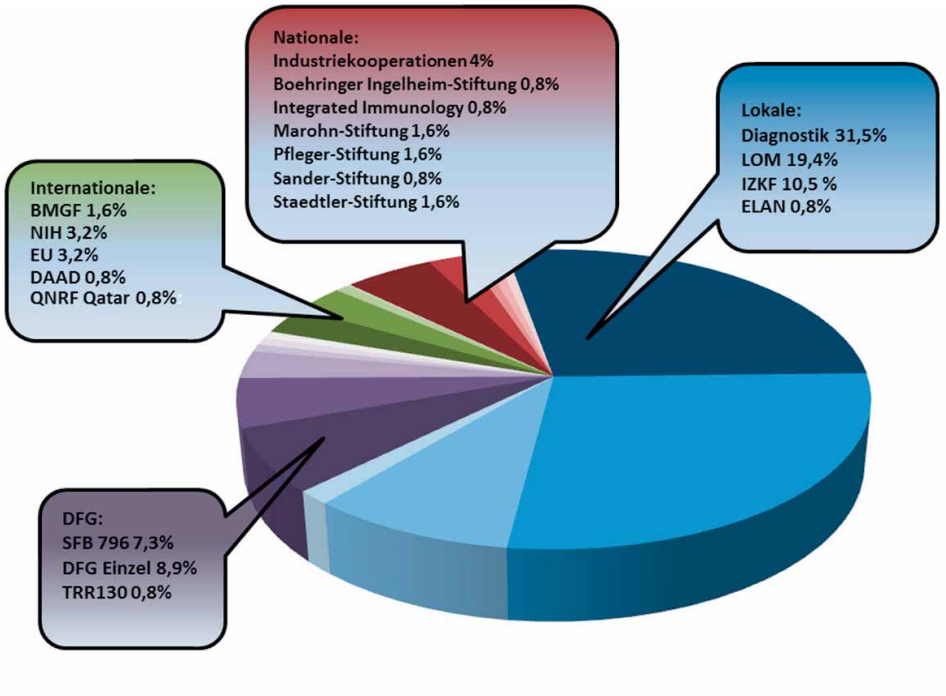
■ Wissenschaftliche Verbrauchsmittel – Supplies



Erläuterung Abkürzungen:

Lokale:	
Diagnostik	Betriebseinnahmen aus klinischer Diagnostik
LOM	LOM-Budget für wiss. Verbrauchsmaterial
IZKF	Interdisziplinäres Zentrum für Klinische Forschung
ELAN	ELAN-Fonds der Medizinischen Fakultät Erlangen
DFG:	**Deutsche Forschungsgemeinschaft:**
SFB 796	Sonderforschungsbereich 796
DFG Einzel	Einzelförderung der Deutschen Forschungsgemeinschaft
SFB TTR130	SFB/Transregio 130
Internationale:	
BMGF	Bill & Melinda Gates-Stiftung
NIH	National Institutes of Health, USA
EU	Europäische Union
QNRF Qatar	Qatar National Research Fund
Nationale:	
Industriekooperationen	Virologik GmbH, MetrioPharm AG, 4 SC AG
Boehringer Ingelheim-St.	Boehringer Ingelheim Stiftung
DAAD	Deutscher Akademischer Austauschdienst
Integrated Immunology	Internationales Master-Programm *Integrated Immunology*/Elitenetzwerk Bayern
Marohn-Stiftung	Johannes und Frieda Marohn-Stiftung
Pfleger-Stiftung	Dr. Robert Pfleger Stiftung
Sander-Stiftung	Wilhelm Sander-Stiftung
Staedtler-Stiftung	STAEDTLER Stiftung
Sonstige	Thyssen-Stiftung, Sammelkonten mit wiss. Verwendungszweck

■ Personalstellen – Personnel Positions



Explanation of abbreviations

Local:	
Diagnostik	Earnings from clinical diagnostics services
LOM	Performance-oriented support system of the Medical Faculty for scientific supplies
IZKF	Interdisciplinary Centre for Clinical Research
ELAN	ELAN Fund of the Medical Faculty Erlangen
DFG:	**German Science Foundation:**
SFB 796	Research Center Grant 796
DFG Einzel	Individual project support of the German Science Foundation
SFB TTR130	Transregional Collaborative Research Center 130
International:	
BMGF	Bill & Melinda Gates Foundation
NIH	National Institutes of Health, USA
EU	European Union
DAAD	German Academic Exchange Service
QNRF Qatar	Qatar National Research Fund
National:	
Industrie-Kooperationen	Cooperation with industry: Virologik GmbH, MetrioPharm AG, 4 SC AG
Boehringer Ingelheim-St.	Boehringer Ingelheim Foundation
Integrated Immunology	International Master programme Integrated Immunology/Elite Network Bavaria
Marohn-Stiftung	Johannes and Frieda Marohn Foundation
Pfleger-Stiftung	Dr. Robert Pfleger Foundation
Sander-Stiftung	Wilhelm Sander Foundation
Staedtler-Stiftung	STAEDTLER Foundation
Sonstige	Thyssen Foundation, general accounts with scientific purpose

N. Lageplan
Location

Sie erreichen uns
Mit dem Zug
Vom Bahnhof Erlangen ca. 10 Minuten Fußweg (Richard-Wagner-Straße, Hauptstraße/Fußgängerzone, Glockenstraße, Theaterplatz, Loschgestraße)

Mit dem Auto
A73 (aus Richtung Bamberg): 1 km Abfahrt Erlangen-Nord: links fahren in Richtung Erlangen Zentrum, auf die Dechsendorfer Straße, dem Straßenverlauf folgen: Martinsbühler Straße, Pfarrstraße, Neue Straße.

A73 (aus Richtung Nürnberg): 1 km Abfahrt Erlangen-Nord: Richtung Erlangen West rechts fahren, nach ca. 400m links in die Martinsbühler Straße einbiegen, dem Straßenverlauf folgen: Pfarrstraße, Neue Straße.

A3 (aus Richtung Würzburg): 10 km Abfahrt Erlangen-West in Richtung Erlangen, Dechsendorf, St. Johann, Dechsendorfer Straße, Martinsbühler Straße, Pfarrstraße, Neue Straße

Neue Straße: Am Katholischen Kirchplatz rechts einbiegen, nach 50 Metern rechts in die Loschgestraße einbiegen, nach 100 Metern erreichen Sie auf der linken Seite den Eingang zum Botanischen Garten und den Fußweg zum Gebäude der Virologie.

Parken:
Der nächste öffentliche Parkplatz ist der Theaterplatz. Weitere Parkmöglichkeiten bestehen im Parkhaus der Uni-Kliniken (Schwabachanlage 14, Zufahrt über Palmsanlage), auf dem Parkplatz Fuchsenwiese sowie am Großparkplatz Innenstadt (von dort 5 bzw. 10 Minuten Fußweg)

How to reach us
By train
Walking distance from the railway station is about 10 min. (1 km). (Richard-Wagner-Straße, Hauptstraße/pedestrian area, Glockenstraße, Theaterplatz, Loschgestraße)

By car
A73 (coming from Bamberg): Exit Erlangen-Nord: turn left in direction „Erlangen Zentrum“ into Dechsendorfer Straße, follow the street on Martinsbühler Straße, Pfarrstraße, Neue Straße.

A73 (coming from Nürnberg): Exit Erlangen-Nord: turn right in direction Erlangen West, turn left into Martinsbühler Straße, follow the street on Pfarrstraße, Neue Straße.

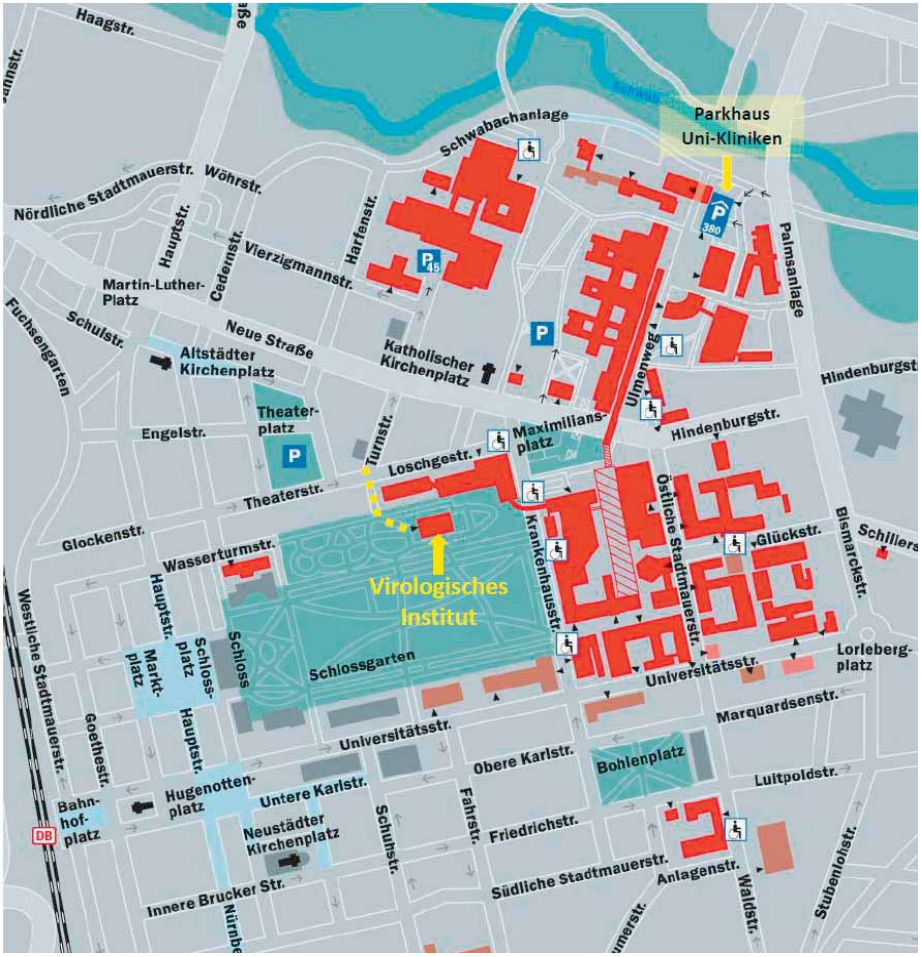
A3 (coming from Würzburg): Exit Erlangen-West in direction Erlangen, Dechsendorf, St. Johann, Dechsendorfer Straße, Martinsbühler Straße, Pfarrstraße, Neue Straße.

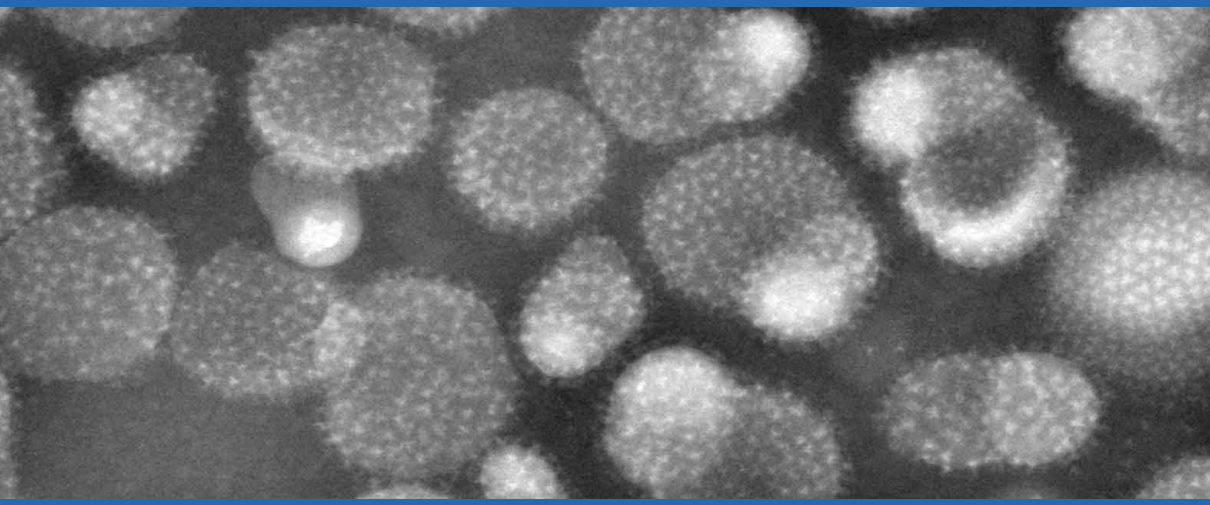
Neue Straße: At the Katholischer Kirchplatz (Church) turn right, after 50 metres turn right into Loschgestraße, after 100 metres you will arrive left of the entrance of the Botanical Garden and the path to the virology building.

Parking:
The next public parking lot is Theaterplatz. Further parkings are the parking garage of the University Hospital (Schwabachanlage 14, access via Palmsanlage), the parking lot Fuchsenwiese and Großparkplatz Innenstadt (walking distance about 5 to 10 minutes)

By plane

Distance Airport Nürnberg/Erlangen approximately 19 km (20 minutes). Please take a taxi and ask the driver to stop in Loschgestraße/corner Turnstraße at the entrance to the Botanical Garden. The department can be reached by car only through Loschgestraße. From the entrance walk a few meters into the Centre of the Botanical Garden, where the Virology building is located.





Universitätsklinikum Erlangen
Virologisches Institut – Klinische und Molekulare Virologie

Schlossgarten 4
D-91054 Erlangen