Programme

Thursday, 6.12.18

9:00 - 9:30 Registration

9:30 - 10:15
K. Hamprecht (Tübingen)
Characteristics of human cytomegalovirus (HCMV) infections in the immunosuppressed patient and in vertical mother-to-infant transmission: impact of viral strain diversity.

10:15 - 10:25
SHORT BREAK

10:25 - 11:20
D. Metzler (Munich)
Computational population genetics and potential applications in virology and cancer biology

11:20 - 11:40
COFFEE BREAK

11:40 - 12:25
I. Görzer (Vienna)
Mixed HCMV strain infections in the human host: An evolutionary advantage in the virus-host interaction?

12:25 - 14:15
LUNCH BREAK

14:15 - 15:00
S. Alizon (Montpellier)
Modelling the evolution of viral oncogenesis

15:00 - 15:10
SHORT BREAK

15:10 - 15:55
N. Lemmermann (Mainz)
The lungs a central organ site of acute and latent CMV infection – what did we learn from mouse models

15:55 - 16:15
COFFEE BREAK

16:15 - 17:45 Discussion session

19:00
WORKSHOP DINNER

Friday, 7.12.18

9:00 - 9:45
J. Leung (Atlanta)
Modeling the control of bacterial pathogens with phage, phage-antibiotic combinations and probiotics

9:45 - 9:55
SHORT BREAK

9:55 - 10:40
S. van Houte (Exeter)
Anti-CRISPR Phages Cooperate to Overcome CRISPR-Cas Immunity

10:40 - 11:00
COFFEE BREAK

11:00 - 11:45
E. Gjini (Lisbon)
New model formalisms for inferring bacterial phenotypic heterogeneity

11:45 - 13:45
LUNCH BREAK

13:45 - 14:30
M. Sieber (Plön)
Modelling the ecology and (co-)evolution of bacteria-phage interactions

14:30 - 14:50
COFFEE BREAK

14:50 - 16:20
Discussion session
led by **O. Krut (Langen)**
Open questions in phage therapy
and **K. Thormann (Gießen)**
Steps towards the (cell-)biology of bacterial phages

Abstracts

Characteristics of human cytomegalovirus (HCMV) infections in the immunosuppressed patient and in vertical mother-to-infant transmission: impact of viral strain diversity.

Klaus Hamprecht
University Hospital of Tuebingen, Germany

Human Cytomegalovirus (HCMV) belongs to the family of human herpesviruses with a linear DNA genome of about 235 Kbp. Herpesviruses induce a persistant infection in their host with a long latency period after primary infection and reactivation under circumstances of temporarily immunosuppression. Human primary infection is mostly mild or asymptomatic. In the transplant setting (solid organ or stem cell transplantation) or untreated HIV patients, HCMV may cause serious life-threathening infections like pneumonia, gastroenteristis or encephalitis. Under unsufficient antiviral therapy or long duration of antiviral treatment, drug resistance in defined target genes (UL97, UL54) may emerge, which leads to the detection of minor mutant viral populations which are able to substitute the wildtype virus completely. Beside immunosuppression, HCMV is involved in prenatal vertical mother to infant virus transmission as the globally most frequent congenital infection or postnatal HCMV infection during lactation. Since HCMV reactivation during lactation has high epidemiological relevance and nearly every HCMV IgG seropositive mother shedds the virus into breastmilk, this phenomenon is a very good tool to study viral reactivation in general. During the process of lactation, viral strains emerge and new strains reemerge with defined changes in surface glycoprotein genes, are transmitted and finally controlled by the immune system of the newborn infant. Especially a risk population of very preterm infants (<1000 g birth weight and $<$ 30 weeks of gestation) may acquire serious and in seldom cases also fatal HCMV infection. Interestingly, it is very easy to isolate viral strains from different compartments like breast milk, amnion fluid, or urine of the infected infants. Dynamics of HCMV reactivation during lactation shows often a unimodal course. The mechanism of the emergence of HCMV shedding is mostly unknown, and the viral decline seems to be mediated by human CMV-specific CD8 T cells.

Computational population genetics and potential applications in virology and cancer biology

Dirk Metzler
Ludwig-Maximilians-University Munich, Germany

Coalescent theory is the basis of many computational methods in population genetics, e.g. to infer population demography or to detect genomic footprints of selection. We discuss some challenges of adapting these methods for inferring parameters of virus evolution and of the clonal evolution of cancer cells in patients after chemotherapy.

Mixed HCMV strain infections in the human host: An evolutionary advantage in the virus-host interaction?

Irene Görzer
Medical University Vienna, Austria

Human cytomegalovirus (HCMV), a member of the betaherpesviruses, is a large dsDNA virus which after infection remains in the human host for a lifetime. At the same time HCMV infections are rarely symptomatic in immunocompetent persons, while they may cause severe illness in congenitally infected newborns or in patients under immunosuppression. Extensive HCMV genome analysis revealed that numerous different HCMV strains circulate in the human population. The linear HCMV genome in virions is about 235 kb in length and consists of about 170 canonical ORFs. About 15% of these ORFs display substantial polymorphic sites and most of these sites cluster into a defined number of so-called genotypes. The characteristic genotypic sequence patterns allow to discriminate the different HCMV strains either by investigating a single locus, multiple loci, or the whole genome. Polymorphic sites are interspersed by highly conserved sequence stretches and linkage among distinct polymorphic loci seems to be rare. This suggests that recombination between different strains has been an important contribution to HCMV strain diversity which, in turn, requires that an individual host is infected with more than one HCMV strain, either simultaneously or serially acquired. So far, there is no clear evidence that naturally occurring HCMV strains differ in their pathogenic potential. However, it appears that polymorphisms in certain HCMV genes may contribute to altered cell tropism or may help to circumvent the HCMV-specific immunological control to facilitate HCMV transmission and reinfection. Consequently, one might hypothesise that the accumulation of more than one HCMV strain within an individual host is fundamental for HCMV persistence in the human population.

Modelling the evolution of viral oncogenesis

Samuel Alizon & Carmen Lia Murall
MIVEGEC, Montpellier, France

Most human oncogenic viruses share several characteristics, such as being DNA viruses, having long (co)evolutionary histories with their hosts and causing either latent or chronic infections. They also tend to cause relative low mortality, which according to virulence evolution theory, makes them quite fit. We use a theoretical evolutionary approach to investigate how the life-cycle from DNA oncoviruses may generate selective pressures within the host favouring or acting against oncogenesis. In particular, we focus on two activities from oncoproteins, namely extending cell life expectancy and increasing cell proliferation rate. These have immediate benefits (increasing viral population size) but can be associated with fitness costs at the epidemiological level (increasing recovery rate or probability of cancer) thus leading to evolutionary trade-offs. Our model allows us to formulate hypotheses regarding cancer as a selective pressure for viruses and to shed a new light on the difference between known oncoviruses.

The lungs a central organ site of acute and latent CMV infection - What did we learn from mouse models

Niels A. Lemmermann
Johannes Gutenberg-University Mainz, Germany

Human Cytomegalovirus (hCMV), the prototype member of the β-subfamily of the herpesvirus family, is a pathogen of high clinical relevance in immunosuppressed patients, e.g. recipients of hematopoietic cell transplantation (HCT), and a causative agent for congenital malformations during pregnancy. After HCT hCMV can cause multiple -organ diseases, interstitial pneumonia in particular, when infection occurs in the period before hematopoietic reconstitution restores antiviral immunity. CMV virus species exist in essentially all mammalian host species and have co-speciated with their respective host in eons of co-evolution, resulting in an intricate virus-host adaptation, reflected on the viral side by sets of "private genes" not shared between different CMV species and resulting in a strict host-species specificity of CMVs. Consequently, no animal model to investigate pathomechanisms of hCMV and to develop strategies for immune intervention exists. Further, the use of heterologous virus-host model would be highly artificial, because the intricate virus-host adaptation by co-speciation would be disrupted. Therefore, the use of homologous models, e.g. rat CMV in rats, is highly recommended. The most used homologous model for hCMV infection is the murine CMV (mCMV) infection of mice, which can mimic many aspects of hCMV pathogenesis, cell / organ tropism, viral latency, immune response, and immune evasion. Here I will present our specialized mouse model of mCMV infection after HCT with focus on antiviral immune control and establishment and maintenance of viral latency.

Modeling the control of bacterial pathogens with phage, phage-antibiotic combinations and probiotics

Chung Yin (Joey) Leung and Joshua Weitz
Georgia Institute of Technology, Atlanta, USA

The rise of antibiotic resistance in common bacterial pathogens is a major public health concern. As such, there is growing interest in the development of effective alternatives and complements to antibiotics. A number of alternative antimicrobial therapies exist, including the use of phage (bacterial viruses) and commensal or probiotic bacteria. However, these therapies have not demonstrated consistent efficacy on par with antibiotics. A possible reason for this inconsistency is heterogeneity in the host immune response against the pathogen. Using a combination of nonlinear population models and animal experiments, we have shown that host immunity works synergistically with phage therapy to cure an acute respiratory infection. As a result of this synergy, the combined action of phage and host immune response can eliminate multidrug-resistant bacteria, even when neither of them can do so when acting alone. Nonetheless, phage therapy could still fail when there is substantial phage resistance in the pathogen inoculum. In such cases, we also consider the combination of phage and antibiotics in enhancing the evolutionary robustness of therapy. Our model predicts that host immunity plays an important role in the efficacy of phage-antibiotic combinations. In particular, in the presence of a competent immune response, a sub-inhibitory dose of antibiotics combined with phage administration is sufficient to robustly eliminate the pathogen population with a

wide range of resistance profiles. Finally, we discuss extensions to our modeling framework to study interactions between host immunity and probiotic therapy by incorporating competition between the pathogen and probiotic bacteria. Our research highlights the need to characterize the host immune status when evaluating the effectiveness of novel antimicrobial therapies.

Anti-CRISPR Phages Cooperate to Overcome CRISPR-Cas Immunity

Stineke van Houte
University of Exeter, England

Bacteria evolve CRISPR-Cas immunity against bacteriophage (phage) by inserting phage-derived sequences into CRISPR loci on the host genome, which can drive rapid phage extinction. Some phages encode anti-CRISPR (acr) genes, which antagonize CRISPR-Cas immune systems by binding components of its machinery, but it is unknown how these acr genes impact phage epidemiology. In my talk I will present experimental data combined with epidemiological modelling predictions to explain how Acr-phages can work together to suppress CRISPR immunity of the host. In the last part of my talk I will discuss ongoing work to understand the long-term maintenance of Acrs in a phage population.

New model formalisms for inferring bacterial phenotypic heterogeneity

Erida Gjini
Instituto Gulbenkian de Ciência, Oeiras, Portugal

Bacterial heterogeneity has been increasingly recognized as a major factor in the failure of antibiotic treatment. One fundamental challenge remains to quantify such heterogeneity, its mechanisms and consequences for the outcome of therapy. In this study I present a modeling framework that accounts for population structure of bacteria undergoing antibiotic treatment at different doses. I will show how we can start to infer and parameterize the underlying phenotypic heterogeneity of the bacterial population, in terms of growth rate and antibiotic resistance, when exploiting the full information in the temporal dynamics. Model results highlight that accounting for phenotypic population structure of bacteria can alter drastically our predictions for therapeutic success.

Modelling the ecology and (co-)evolution of bacteria-phage interactions

Michael Sieber
Max Planck Institute for Evolutionary Biology, Plön, Germany

I will showcase the value of combining experimental and modelling approaches to understand bacteria-phage interactions. Starting with a relatively simple system of two bacteria associated with the Hydra microbiota, I show how modelling both the lytic and the lysogenic life cycles of a phage provides an explanation for the experimentally observed curious interaction between the two bacteria. And since microbes typically live in spatially extended habitats, I then move on to address how dispersal between different habitats can influence host diversification during coevolution between bacteria and phages. I round off my talk with

some theoretical work on intrinsic features of the phage life-cycle, which can limit host range evolution without the need to invoke usual trade-offs.

Steps towards the (cell-)biology of bacterial phages

Kai Thormann
Justus-Liebig-University Gießen, Germany

Discovered more than 100 years ago, research on phages and their interaction with the bacterial host revolutionized our understanding of the molecular principles of life. However, our understanding of phage biology is restricted to very few model system phages, such as the Escherichia coli phages T4, Lambda, Mu, or T7. Next-generation sequencing of new phage isolates as well as metagenomics approaches has led to a massive expansion of the phage genomic space. However, still the majority ($> 80\%$) of phage-encoded gene functions remains completely unknown, demonstrating that we basically have no idea how these phages function. Recently, work on non-model phages led to the discovery of new concepts in phage biology. This and the availability of more advanced techniques, e.g. in microscopy, prompted us to attempt the application of bacterial cell biology approaches also for phages in our model species, Shewanella. We have now established genetic and microscopic techniques for non-virulent lysogenic phages and are currently expanding this toolset also for virulent phage isolates and other species, which we will further use to increase our understanding of phage-protein function and phage-host biology.

Open questions in phage therapy

Oleg Krut
Paul-Ehrlich-Institute, Langen

The rise of multi-resistant bacterial pathogens unsusceptible to conventional antibiotic therapy urgently requires the development of alternative therapeutics. The potential of bacteriophages has been implicated by accumulated clinical experience especially in Eastern European countries. However, clinical studies according to Western standards have only be initiated recently, so that safety and efficacy of phage preparations still has to be established for a number of indications, before licensing of such preparations can be pursued. The nature of bacteriophages with regard to the anticipated therapeutic effects raises a number of open questions to be addressed in drug development: resistance development, phage-host interaction in complex matrices, role of immune system, engineering approaches etc. Many of these questions might be addressed by mathematical approaches.