

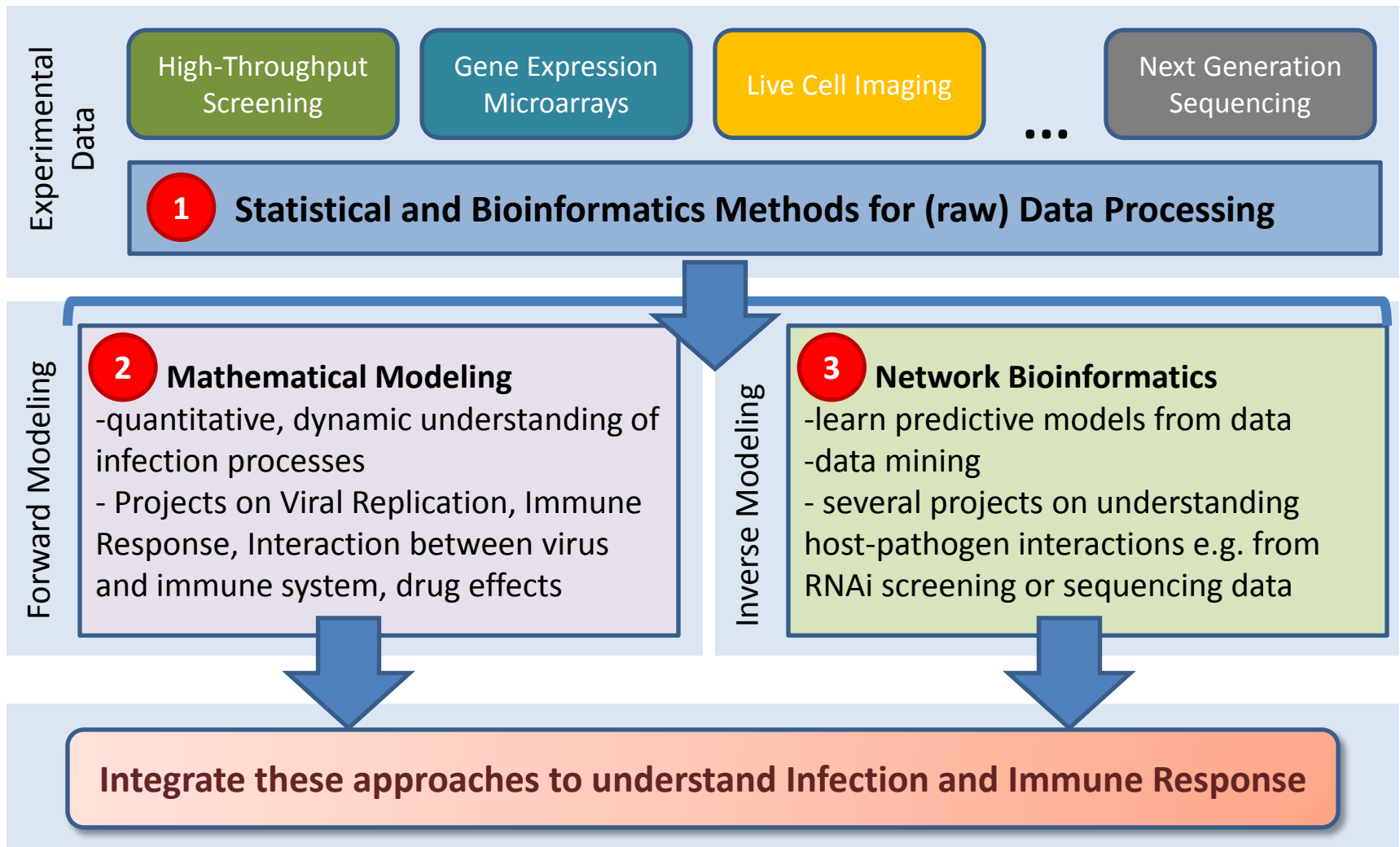
AG Kaderali Bioinformatics / Mathematical Modeling of Infection

Prof. Dr. Lars Kaderali
Hiddensee, October 27, 2015



Institut für Bioinformatik

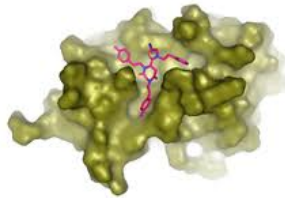
Research Overview



SysVirDrug: Novel Antiviral Drugs!

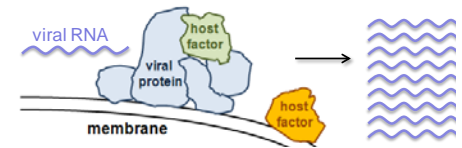
Most antiviral drugs inhibit viral enzymes

- Spectrum of activity?
(may not target all types)
- Development of resistance
- Less chance of side-effects

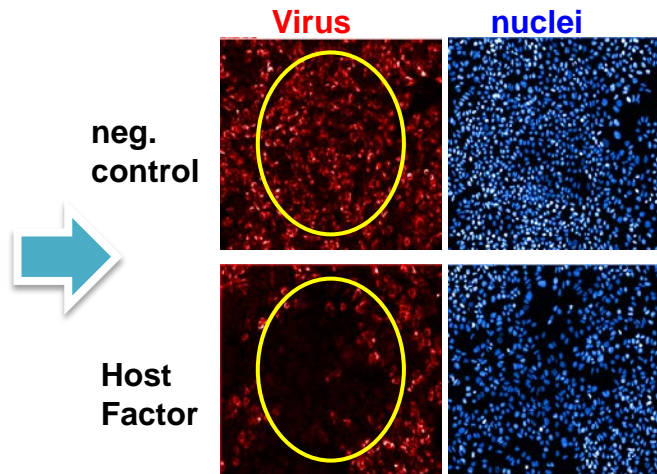
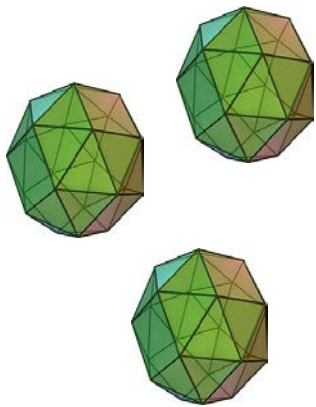


Growing interest in developing inhibitors of essential host factors

- Broad spectrum (related viruses use common replication strategy)
- Host factors unlikely to become resistant
- Side-effects?

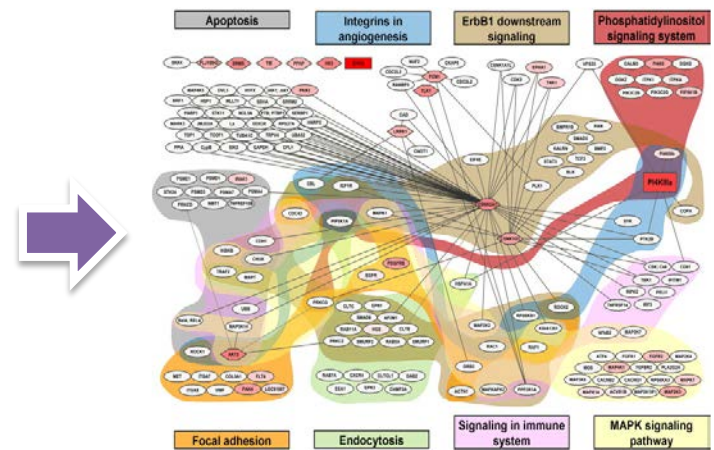


RNAi to Identify Host-Pathogen Interactions



- Hepatitis C virus
- Dengue virus
- SARS-coronavirus
- Chikungunya virus
- Enterovirus (Coxsackie B3)

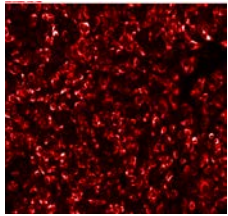
- High-throughput, siRNA-based Screening



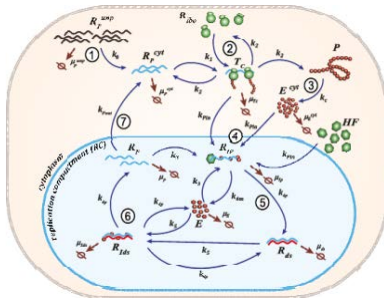
- Sophisticated, network- and pathway-based Bioinformatics Analysis

Reiss, Woerz et al., Cell Host&Microbe 2011
Pönisch et al., PLoS Pathogens, 2015
Amberkar&Kaderali, BMC Alg Mol Biol, 2015

Model Analysis and Inhibitor Design

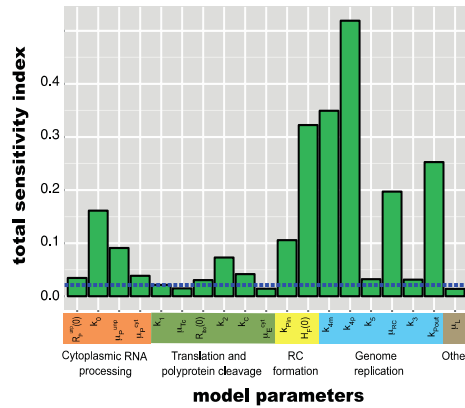


Host Factors



Mathematical Model

Model Analysis

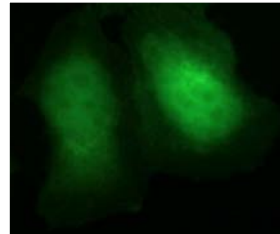


Virtual screening



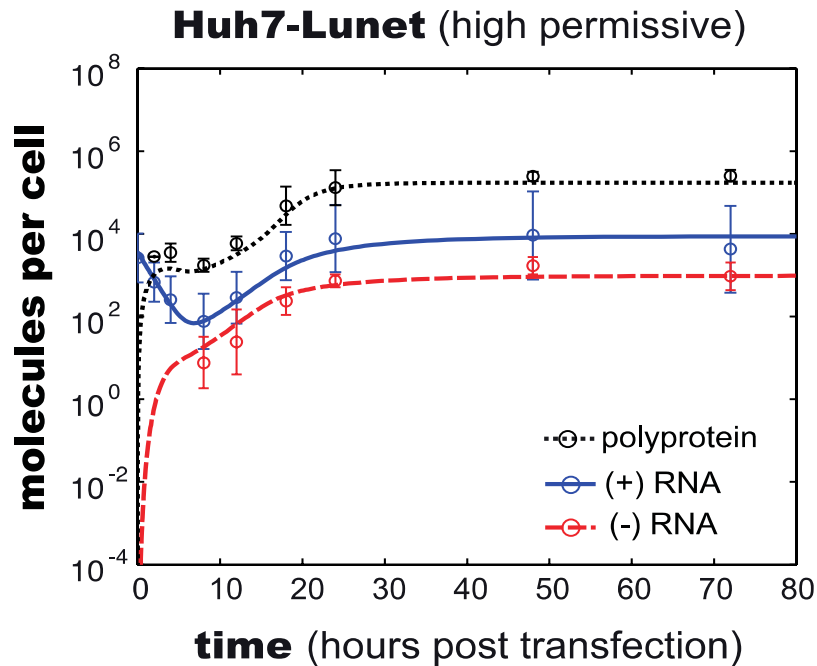
Antiviral Compounds

Experimental Validation

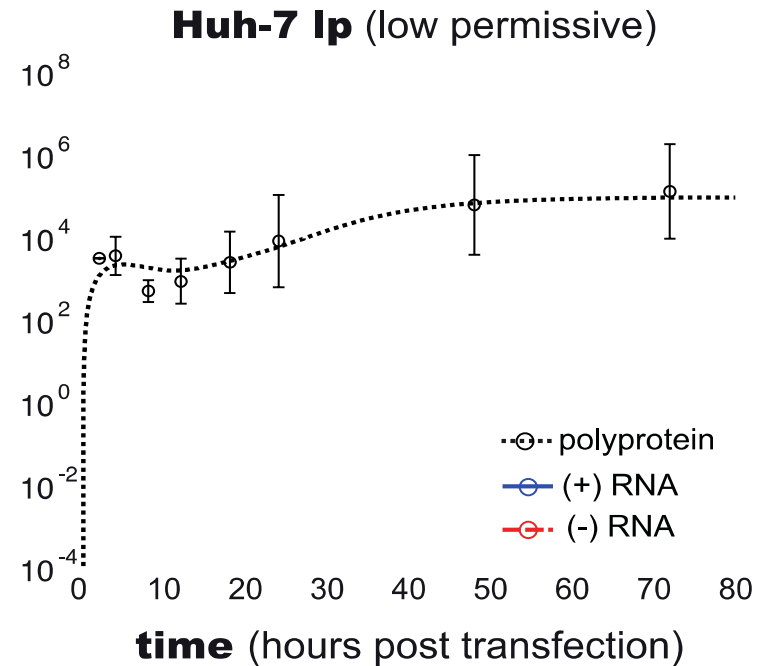


Mathematical Model to Explain Differences in Cellular Hep-C Virus Replication Permissiveness

A



B

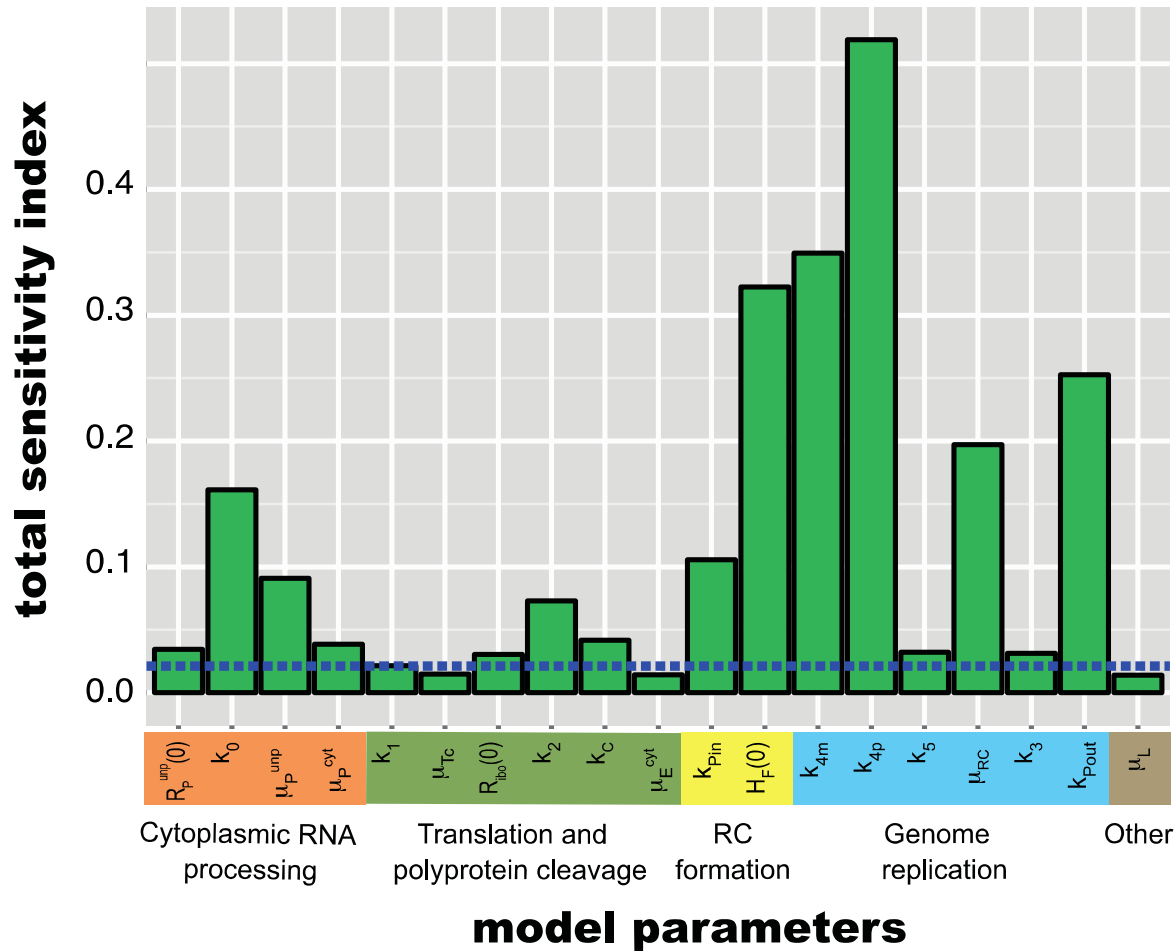


Difference in replication in high and low permissive cells is explained by the different expression level of a host factor which participates in the formation of replication vesicles

Sensitivity Analysis

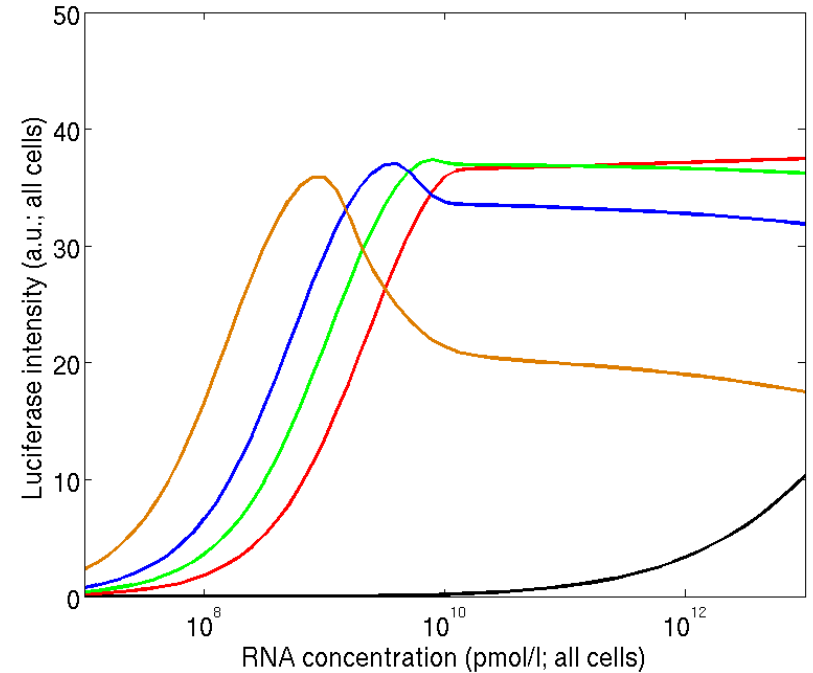
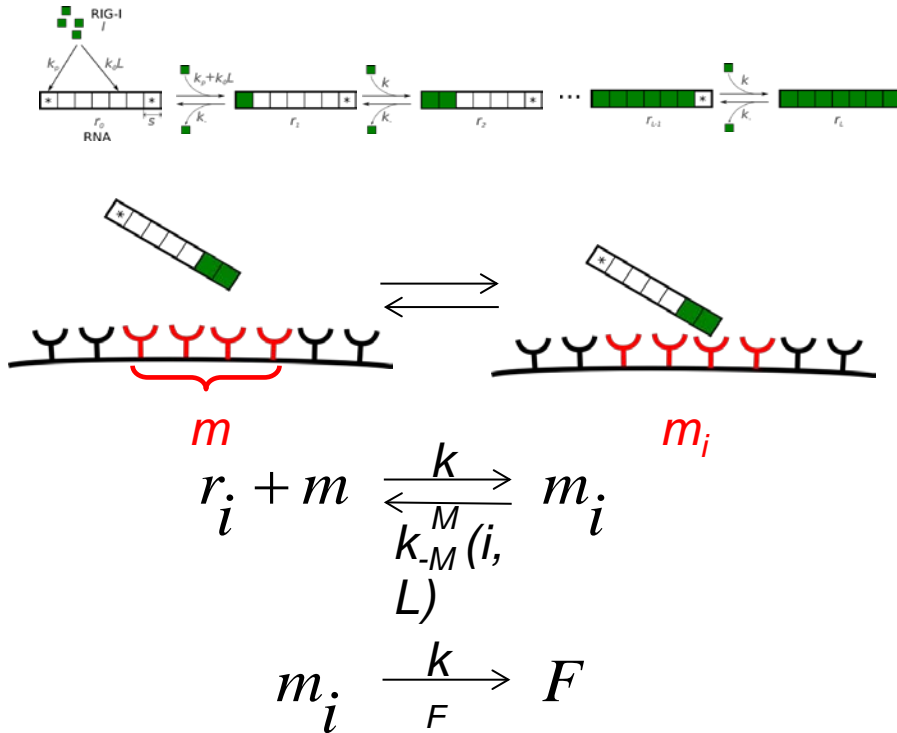
A

plus-strand RNA (4 h post transfection)



Interference with RNA polymerization is significantly more potent than impeding protease activity!

Modeling Innate Immune Recognition

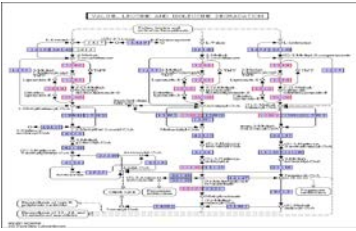


— 1600 bp — 400 bp — 200 bp
— 100 bp — 40 bp

Cooperativity of the Rig-I RNA binding reaction underlies nonlinear features of pathway activation

Outlook: Systems Biology of Infection

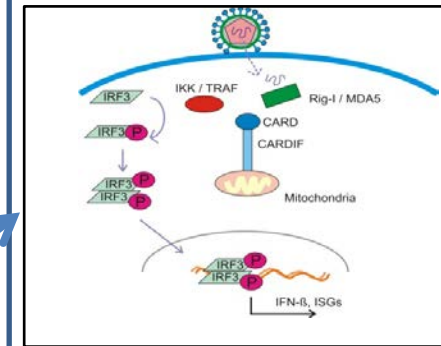
Host Factors



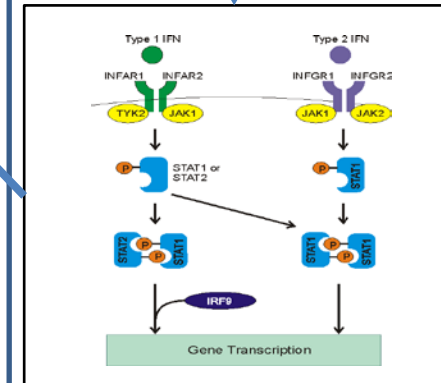
PK / PD Models



Innate & Adaptive Immune Response

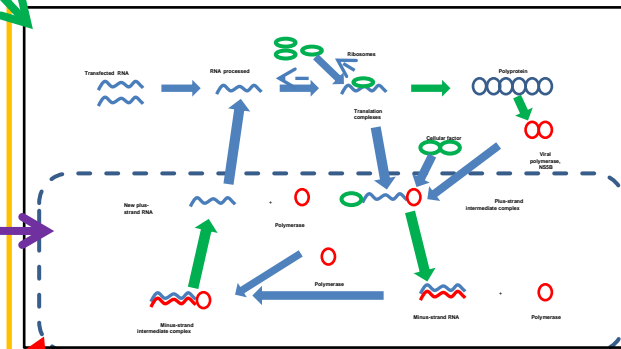


RIG-I Pathway

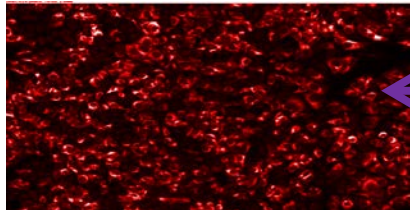


Jak/Stat Pathway

Viral Life Cycle Model



Cell Populations, Tissues, Organs, ...



Clinical Data



- Influence of additional host factors
- Comparison accross different viruses
- Optimization of Intervention Strategies (Drug Combinations)
- PK/PD models

Possible Collaborations

What we can offer

- High-throughput data analysis (biostatistics, bioinformatics)
- Data integration, data mining on infection processes
- Mathematical modeling of infection and immune response
- Computer simulations of infectious processes, mathematical modeling and model analysis to generate / test hypotheses about mechanisms

What we are looking for

- New collaborations in particular with experimental / virological / immunological partners on elucidating host-pathogen interactions
- High-Throughput (“global view”) data for bioinformatics analysis
- Detailed dynamic data for development of kinetic mathematical models
- So far worked with viruses, many of the methods and tools used should be transferable to bacteria