Universität Basel

Research Project

TargetInfectX – Multi-Pronged Perturbation of Pathogen Infection in Human Cells

Third-party funded project

Project title TargetInfectX – Multi-Pronged Perturbation of Pathogen Infection in Human Cells
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Status Completed

To uncover the human protein network underlying infection and to identify targets for novel host-directed antiinfectives, ***InfectX*** (20092013) employed RNA interference (RNAi) screens. In that project, libraries of small inhibitory RNAs (siRNAs) that systematically target a large fraction of human genes were screened, and the effects of individual siRNA perturbations on the cellular infection processes by various human pathogens were measured. The imagebased highcontent RNAi datasets that were generated through a standardized experimental and computational approach are of unprecedented quality and breadth and should thus enable systemslevel analyses of general genephenotype relationships. SiRNAs are designed to be perfectly complementary to 19 23 nucleotide regions in the intended mRNA targets. As siRNA targets undergo degradation upon siRNA transfection, it is generally assumed that the observed phenotypes are due to the direct effect of the siRNA on these targets (‘ontarget effect’). However, our systematic exploration of the impact of siRNAbased RNAi on two phenotypic readouts (cell number and infection index) in ***InfectX*** has highlighted the prevalence and magnitude of ‘offtarget effects’ that are mediated by the siRNA ‘seed sequences’ (nucleotides 28 from the 5’ end of the siRNA) through a microRNA (miRNA)type mechanism. A major contribution that ***InfectX*** made to the RNAi screening field was the development of modeling approaches to comprehensively quantify offtarget effects, partly deconvolute combinatorial effects, and finally provide improved methods for establishing individual genephenotype relationships. The present proposal, ***TargetInfectX*** (20142017), will build on the imagebased highcontent RNAi datasets established within ***InfectX***, but will have more farreaching goals. From the image data generated in ***InfectX*** we will extract a rich set of phenotypic features on the singlecell level. Modeling miRNAtarget mRNA interactions, their effect on gene expression, and the genephenotype relationships emerging from the imaging data, we will attempt to generally reconstruct the genotypic basis of elementary cell behaviors such as those involved in the response to pathogen intrusion. On the translational side, we will explore the potential of siRNAs as novel combination therapy approach to interfere with the course of infections. Moreover, beyond the public release of our data via publications and publically accessible databases, we will encourage knowledge and technology transfer

of unpublished work in progress with partners outside of ***TargetInfectX*** via a collaboration suite that should foster longterm collaborations and ensure the impact of our work beyond ***SystemsX.ch***.

Keywords Bacterial infection, RNA interference, miRNA, seed sequence, Computational network modeling, Signaling pathway reconstruction, Anti-infective
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Add publication

Published results

3775471, Riba, Andrea; Emmenlauer, Mario; Chen, Amy; Sigoillot, Frederic; Cong, Feng; Dehio, Christoph; Jenkins, Jeremy; Zavolan, Mihaela, Explicit Modeling of siRNA-Dependent On- and Off-Target Repression Improves the Interpretation of Screening Results, 2405-4712 ; 2405-4720, Cell Systems, Publication: JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

Add documents

Specify cooperation partners

ID	Kreditinhaber	Kooperationspartner	Institution	Laufzeit - von	Laufzeit - bis
4235359	Zavolan, Mihaela	Jenkins, Jeremy	Novartis Institute for Biomedical Research	01.04.2014	31.12.2030