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Dual targeting of the host-pathogen interface: Bacterial release and selective cytotoxicity

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A critical feature of the Mycobacterium tuberculosis bacillus is its ability to survive within macrophages, making these host cells an ideal niche for persisting microbes. Identifying inhibitors of *M. tuberculosis* intracellular growth from large chemical library has long been hampered by labor-cumbersome techniques. We thus developed a phenotypic cell-based assay relying on automated confocal fluorescence microscopy and adapted it for the high throughput screen of compounds that interfere with the multiplication of *M. tuberculosis* within macrophages. The current project is an early drug discovery that uses alternative drug screening strategies and targets previously unexplored biological activities during tuberculosis (TB) infection. The aim of the project is to establish a novel approach within the host pathogen interaction paradigm. The approach is based on identification of the drugs and cellular pathways that trigger active bacterial release form its host into the extracellular space or by specific killing of infected host cells. Both of these strategies can prevent the infection from spreading. Such drugs and pathways might also facilitate the boosting of the immune response and enhance the effect of other conventional antitubercular compounds. To reach our goal we established a high though put assay that uses a host-pathogen system based on human cultivated macrophages and Mycobacterium tuberculosis H37Rv to test the activity of the drugs at the single cell level. Screening will be followed by drug synergy studies with the use of known antitubercular compounds. Subsequently, studying the drug mechanisms of action will be performed with cultivated macrophages.

Biography

Valentin Trofimov has his expertise in high-content and high-throughput drug screening. He aims to help eradication of the threat of tuberculosis worldwide. Tuberculosis (TB) results in the death of millions of people every year. There is a growing threat because of the emergence of multidrug resistant strains. In order to achieve that goal, new effective drugs and efficient TB therapies need to be discovered. He focuses his effort on early drug discovery with a close look at host-pathogen interactions, since in vivo activities, such as intracellular host defense mechanisms, are largely overlooked in drug research.

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