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Potential Ebola therapies identified using high throughput phenotypic screening of drugs and combinations

Gene Olinger[2], B.G. Hoffstrom[1], A. Stossel[2], C. Scully, J. Brannan, D. Julias[2], C. Lear, J. Lehár[1], L. M. Johansen[1] and L. Hensley[2]

[1]Zalicus, Inc, Cambridge, USA
[2]The United States Army Medical Research Institute of Infectious Diseases (USAMRIID), USA

To date, Ebola lacks licensed vaccines or therapeutics for prophylaxis or post-exposure treatment. Phenotypic screening of approved drugs can discover therapies that can be quickly deployed, and which often target host factors. We assembled a library of about 3,000 approved drugs and biologically active molecules, and tested them at multiple concentrations for antiviral activity using VERO cells infected with an engineered GFP-expressing Ebola virus. Hits were selected using both activity measurements and clinical safety information, and comparisons between agents targeting the same protein were used to distinguish on- vs. off-target effects. We identified ~130 potential therapies with selective antiviral activity on ~50 distinct mechanistic classes. Thirty compounds were prioritized for active combination screening which resulted in 435 unique pair-wise combinations. Many of the antiviral activities discovered involve host cell mechanisms with previously unknown relevance to filovirus infection, including estrogen receptor antagonists and calcium channel blockers. We identified many synergistic or additive drug combinations, five of which yielded over tenfold increases of potency over the single agent activity. Results in a mouse Ebola infection model confirm that many of the mechanistic classes identified have protective antiviral effects including estrogen receptor antagonists, calcium channel blockers and drugs with CNS indications. The drugs identified show translation in animal models supporting the potential of developing these drugs for clinical use. In addition to discovering novel viral-host mechanisms, testing these drugs in combination has revealed unforeseen drug synergies that can substantially improve therapeutic selectivity and limit the emergence of resistance.

Biography

Dr. Olinger is the principle investigator of several projects focused on the development of countermeasures against highly lethal viral hemorrhagic fever viruses (VHFV). His team works on the development of vaccines and therapeutics for VHFV, specifically Ebola and Marburg viruses. Dr. Olinger has a Ph.D. in immunology and virology from Rush University in Chicago, IL and was awarded a post-doctoral research fellow with the National Research Council working at USAMRIID. Dr. Olinger has served as a subject matter expert for multiple DOD and Federal panels related to biodefense and serves as an NIH review for HIV SBIR & STTR research.