Large Scale Screening and Identification of Novel Ebolavirus and Marburgvirus Entry Inhibitors

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Filoviruses are highly infectious, with no FDA-approved drugs available for their treatment. The last Ebola virus outbreak killed about 11,000 people and highlighted the lack of and a need for new anti-filoviral drugs and therapies. Most efforts to find such drugs have involved only a few strains of Ebola virus and testing relatively small drug libraries or compounds that have shown efficacy against other viruses or diseases. A requirement to handle these viruses at biosafety level 4 (BSL-4) is another bottleneck in these efforts. Here we report the first and largest high-throughput screening of 319,855 small molecules from the MLSMR library against Marburg virus and Ebola virus. We developed and used a quantitative, high throughput screening platform based on high resolution microscopy to determine the mechanism of action of entry inhibitors. Nine of the most potent, novel compounds that blocked infection by both viruses were analyzed in detail using this platform. The compounds inhibited known key steps in Ebolavirus infection mechanism by blocking either cell surface attachment, macropinocytosis-mediated uptake or endosomal trafficking. Each inhibitor was active in primary human macrophages thereby demonstrating their potential to be developed as drugs.