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In silico prediction of influenza interaction sites with host cells using an artificial phage display evolution system

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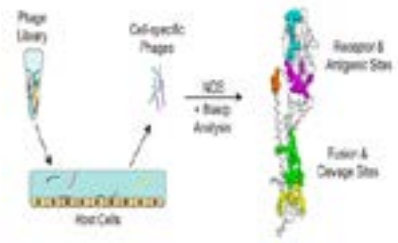
Viruses lack the ability to replicate without a host. Therefore, to ensure replication and continued persistence in an environment they must acquire mutations in their capsid proteins, through natural selection, to allow specific interactions with receptors expressed on a host cell. These interaction sites are ideal targets for vaccine development or therapeutic drug development, but identification can be time consuming or highly variable due to antigenic drift and rapid mutation rates of the virus. The filamentous bacteriophage, fd, has no natural tissue tropism to mammalian cells, but can be engineered to display short peptides fused to the 4,000 copies of its major coat protein. We hypothesize that these engineered phages can be used to predict interaction sites of natural viruses with a host. Here, we enriched for a sublibrary of phage clones that interact with small airway epithelial (SAE) cells from a multi-billion phage library and identified the recovered sequences by next-generation sequencing (NGS). Representative consensus sequences for influenza hemagglutinin (HA) and neuraminidase (NA) proteins were generated using the NCBI Influenza Virus Resource. Using blastp with settings optimized for short peptides, the resulting sequences were searched against our recovered phage sublibrary interacting with SAE cells. Several peptides with high structural homology to either influenza structural proteins were identified. The recovered peptides were found near previously identified functional domains including, the membrane fusion domain and the HA0 cleavage site of HA. Additional domains were identified suggesting residues that may be involved with a co-receptor binding site. Here, we justify the use of phage display as an artificial evolution system in combination with next generation sequencing datasets to identify virus-host interaction sites based on the protein sequence of the virus. This technique can be extended to broader applications to rapidly identify interaction sites of novel pandemic or high-risk viral pathogens.

Image:



Recent Publications:

1. Petrenko VA, Gillespie JW (2016) Paradigm shift in bacteriophage-mediated delivery of anticancer drugs: from targeted 'magic bullets' to self-navigated 'magic missiles'. Expert Opin Drug Deliv. 2016 Aug 5: 1-12.
2. Gillespie JW, Wei L, Petrenko VA (2016) Selection of lung cancer-specific landscape phage for targeted drug delivery. Comb Chem High Throughput Screen 19(5): 412-422.
3. Gillespie JW, Gross AL, Puzyrev AT, Bedi D, Petrenko VA (2015) combinatorial synthesis and screening of cancer cell-specific Nano medicines targeted via phage fusion proteins. Front. Microbiol. 6:628. doi: 10/33.89/fmicb.2015.00628
4. Wang T, Yang S, Mei LA, Parmar CK, Gillespie JW, Praveen KP, Petrenko VA, Torchilin VP (2014) Paclitaxel-loaded PEG-PE-based micellar nanopreparations targeted with tumor-specific landscape phage fusion protein enhance apoptosis and efficiently reduce tumors. Mol. Cancer Ther. 12:2864-2875. doi: 10.1158/1535-7163.MCT-14-00

Biography

James W. Gillespie graduated from Auburn University with a BS in Biochemistry (2007) and completed a Ph.D. in Biomedical Sciences (2015). In 2016, he joined the faculty of the College of Veterinary Medicine at Auburn University as a Research Assistant Professor. He has served as Key Personnel and Co-PI on grants from the NIH-NCI and AURIC. He is a member of the American Association of Pharmaceutical Scientists (AAPS), American Chemical Society (ACS), Auburn University Research Initiative in Cancer (AURIC), and the National Cancer Institute Alliance for Nanotechnology in Cancer (2009-2015). His current research interests include phage display, development of precision nanomedicines, and prevention/diagnosis/treatment of neoplastic and infectious deceases.

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