Reem Al Olaby, J Biotechnol Biomater 2015, 5:7
http://dx.doi.org/10.4172/2155-952X.C1.046

OMICS International
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412th OMICS International Conference
World Bio Summit & Expo
November 02-04, 2015 Dubai, UAE

A promising drug lead that inhibits HCV infectivity in a genotype-independent manner

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E2 glycoprotein plays a significant role in the HCV life cycle, but only crystal structures of short peptides, or epitopes were present until Kong et al. resolved the new HCV E2 core (E2c) crystal structure. We have created a new HCV E2 homology model based on the new E2c crystal structure, selected 3 potential binding sites located near residues critical for HCV entry, and used computer docking to identify a set of ligands that should bind to the sites. We tested the set for E2 binding using surface plasmon resonance and performed inhibition assays of HCV infection. One of these compounds, E2216, inhibited HCV infectivity. The homology model was created using AS2TS and Smith-Waterman, FASTA, BLAST and PSI-BLAST sequence alignments. Three potential ligand-binding sites were selected and 3 corresponding grid parameter files were created using Autodock 1.5.6 to guide the virtual screening of ~4,000 ligands (NCI_DSII library). Recombinant HCV E2 protein was used to identify 40 virtual screening hits by using Biacore t100. Pseudotyped retroviral particles harboring HCV envelope proteins (HCVpp) of genotype 2a and cell culture-produced HCV particles (HCVcc) based on the JFH1 strain were used in testing the ligands for HCV infectivity inhibition. E2216 was observed to selectively block the HCV infectivity of both HCVcc and HCVpp with an IC50 of 6.2uM and 3.3uM respectively in a genotype-independent manner. It was also found to block the cell to cell transmission. E2216 appears to be a promising drug lead that targets HCV E2 and can be further optimized to help in blocking HCV entry into hepatocytes and prevent the progression of the infection.

Biography

Reem Al Olaby has a Bachelor in Pharmaceutical Sciences, an MSc in Biotechnology and a PhD in Applied Sciences from The American University in Cairo. She has one full US-PTO patent and 2 provisional patents for identifying several drug leads against HCV and Malaria. She is currently a merit Scholar at the Master's of Public Health Program at George Washington University and is willing to bridge the gap between scientific research, industry and public health as an optimum major goal. She is currently working as a Postdoctoral Research Associate at Qatar University and Health Projects Consultant and OPMC.

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