Title of the Thesis: Assessing genetic diversity of the circulating A/H1N1pdm09 in Eastern India: Identification and characterization of synthetic small molecules as potential antiviral therapeutics

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Influenza viruses are more closely associated with winter; the local climate/habitat and geography sometimes differentiate this tendency. The symptoms include fever, sore throat, headache, dry chough, nasal discharge depending on the nature of the infection, and may end up in severe complications, particularly in those who are at risk like pregnant women, infants, elderly and immunocompromised individuals. The antigenic variation is rapid and occurs through antigenic drift and shift where new strain emerges with pandemic causing potential. Even with improvised vaccination and widespread use of antivirals, influenza continues to challenge the global health community. The genus Orthomyxoviridae includes the virus which is of 4 types (A, B, C and D) with only types A and B cause epidemics. The virus has eight single-stranded RNA fragments coding for eleven proteins.

A retrospective analysis of A/H1N1pdm09 positivity rates in eastern India during April' 2017- March' 2019 showed a remarkable reduction compared to prior influenza outbreaks. In contrast to high incidence of influenza activity in winter and spring, we noted no seasonality pattern of virus activity possibly of passive surveillance where only severe cases are referred to laboratories for testing. Sequencing data revealed novel glycosylation sites and amino acid substitution in hemagglutinin (HA). In contrast, no classical mutations implicated in antiviral resistance was observed in neuraminidase (NA). Phylogenetic studies revealed that majority of circulating strains were similar to the currently used vaccine strains. The study led to the conclusion that influenza vaccination policy for whole nation is necessary, especially for groups which are exceptionally high-risk due to recurring outbreaks in the country.

The continuous evolution of influenza viruses due to antigenic shift and presence of large number of HA and NA subtypes have made developing effective antivirals a challenging task. Introduction of mutations have reduced the efficacy of NA inhibitors and M2-ion channel blockers. Thus, there is continuous need to develop new antivirals. Currently the focus is on drug repurposing and on developing active phytochemical from natural resources. This study has tried to exploit both avenues. Minocycline, which is a tetracycline analogue, was studied for its anti-influenza activity. Minocycline showed potent anti-influenza activity both in vitro and in vivo at non-toxic doses. Minocycline exerted its antiviral activity by integrating both inhibition of late-stage apoptosis and suppressing the phosphorylation of ERK which inhibited the export of viral ribonucleoproteins (vRNPs) from the nucleus, which is an essential process for viral assembly and release. It may thus be proposed that minocycline may act as an antiviral drug. Using FDA approved drug minocycline in a new way brings an exciting prospect for influenza therapy.

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24/6/24

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