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ASIA EDITION

Target for potent first-strike influenza drugs identified

August 3, 2012 | News | By BioSpectrum Bureau

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Singapore: Scientists at St. Jude Children's Research Hospital have reported details of how certain drugs can precisely target and inhibit an enzyme essential for the influenza virus replication. Since all strains of the virus require the same functioning enzyme, researchers believe their findings will yield drugs that can effectively treat new strains of the virus, which may be resistant to current antiviral treatments.

When new strains of influenza emerge, it can take many months for a vaccine to be developed. Experts are concerned that the emergence of any highly virulent strains could result in large numbers of people being hospitalized, and if the strain is or becomes resistant to current treatments, the impact could be catastrophic. The researchers' findings may lead to the ability to develop drugs that not only treat influenza but impede the ability of the virus to develop drug resistance. The study appears online in the August 2 issue of PLoS Pathogens.

St. Jude scientists tested drugs aimed at blocking a dual-purpose enzyme complex, called a polymerase, produced by the influenza virus. This polymerase produces copies of the viral genome during replication. It also assembles molecules called messenger RNA (mRNA) that code for viral proteins the virus needs to hijack the cell's machinery to make it produce more virus.

The drugs that investigators tested target an RNA-snipping enzyme called an endonuclease that is a key subunit of the polymerase complex. The endonuclease enables the virus to disguise its messenger RNA so it will be incorporated into the cell's protein-making machinery. This masking consists of snipping apart cellular mRNA, but retaining a segment called a "cap" that the cell's machinery uses to identify its mRNA. The polymerase then attaches this cap to its own mRNA.

"Inhibitors of the polymerase complex would make excellent drug candidates," said Stephen White, DPhil., chair of the St. Jude Structural Biology department and the study's senior author. "It is a good target because these polymerases are

essentially the same across many strains, and also because the virus absolutely needs the polymerase to make copies of itself. The polymerase doesn't have very many similarities to other polymerases in cells, so it should be fairly specific for the flu polymerase."