

Invited Talk

**SARS molecular epidemiology and SARS-CoV evolution:
Combating an emerging infectious disease
with the regimen of genomics and bioinformatics**

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The prompt identification of a novel human coronavirus as the etiologic agent of severe acute respiratory syndrome (SARS) and the following characterization of its genomic sequence demonstrated the power deriving from coordinate integration of clinical investigation, molecular virology studies and genomic sequencing efforts. The foresight in saving specimens of both human and animal origin from the critical early stages of two SARS outbreaks (2002-03 and 2003-04) and the strategic and methodological break-through in bioinformatics analysis led to the systematic study of multiple viral genomic sequences together with high quality epidemiology information. The viral genomic evolution studies enabled us to reveal the strong adaptive selection pressures initially influencing the SARS coronavirus (SARS-CoV) in both human and animal hosts until a stable genotype that evolved to predominate the later part of the 2002-03 epidemics. This study also supported the zoonotic argument of SARS and indicated that Himalayan palm civets (*Paguma larvata*) of the Guangdong game-market are important vectors of SARS-CoV, facilitating the viral tropism transition and the initiation of the human epidemic. Combining the information of computer simulated S protein structure and its ACE2 receptor binding domain (RBD), major genetic variations in the S gene, which seemed essential for the transition of SARS host tropism, were identified. Based on the pseudo-typed virus infection experiments, the K/R479N and S487T variations in RBD are proved to be critical for efficient human ACE2-dependent cell entry, which led to the hypothesis of a double-substitution strategy responsible for the host transition and adaptation of SARS-CoV that eventually caused the first SARS human epidemic of 2002-03. The lessons and experiences learnt from the SARS molecular epidemiology and SARS-CoV molecular evolution studies could be applied in the research of avian influenza and other emerging infectious diseases.