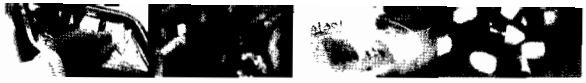

Keynote Lecture XIII

Crystal Structures of SARS Coronavirus Proteins

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Zihe Rao received his PhD in 1989 from St Vincent's Institute of Medical Research & Department of Biochemistry, Melbourne University. He was engaged in postdoctoral research work from 1989 to 1996 with Professor David Stuart in the Laboratory of Molecular Biophysics, University of Oxford. From 1996 until present, he holds the positions of Professor and Head of the Laboratory of Structural Biology, Tsinghua University. From March 2003 until present, he holds the position of Director-general of the Institute of Biophysics, Chinese Academy of Sciences. In July 2003, he was appointed Director of the key National Laboratory of Biomacromolecules. From March 2004 until present, he holds the position of Vice-dean of the School of Life Science and Medicine in Tsinghua University. In 2003, he was elected as a Member of the Chinese Academy of Sciences. In 2004, he was elected as a Member of the Third World Academy of Science.

Zihe Rao is mainly engaged in the study of the three-dimensional structures of significant proteins related to human disease or with important physiological functions, as well as in proteomics and innovative drug design. To date he has published more than 142 peer-reviewed papers in international scientific journals such as *Cell, Nature, PLoS Biology, PNAS, J Biol Chem, J Mol Biol, J Am Chem Soc* and so on.

Professor Zihe Rao attained the Hong Kong "Qiushi Outstanding Scientist Prize in Life Sciences" in 1999, and in 2000 was appointed as a "Yangtze River Distinguished Scholar" professor by the Ministry of Education. In 2003 he received the "He Liang Heli Foundation Science and Technology Prize".

Since the 2003 SARS outbreak, which has now subsided, our laboratory has taken a "structural proteomics" approach to the SARS coronavirus (SARS-CoV). A series of important results in SARS basic research can be summarized as follows:

The structure of the SARS coronavirus main protease (Mpro or 3CLpro) and its complex with an inhibitor were determined by our group in 2003. A key enzyme in viral gene expression and replication, the Mpro was the first SARS-CoV protein structure to be determined in the world and is an important target for anti-SARS drug design. CoV main proteases were revealed to share a highly conservative substrate-recognition pocket by comparison of four crystal structures and a homology model representing all three genetic clusters of the genus Coronavirus. Mechanism-based irreversible wide-spectrum inhibitors were designed with fast in vitro inactivation of multiple coronavirus Mpros, potent antiviral activity, and extremely low cellular toxicity in cell-based assays.

The second crystal structure determined by our group is the SARS-CoV spike (S) protein fusion core. The S protein fusion core is characterized by two heptad repeat (HR) regions, HR1 and HR2. The SARS-CoV fusion core protein structure is a six-helix bundle with three HR2 helices packed against the hydrophobic grooves on the surface of a central coiled coil formed by three parallel HR1 helices in an oblique antiparallel manner. We also determined the mouse hepatitis virus (MHV) S protein fusion core and proposed a conserved molecular mechanism by which the S protein mediates CoV membrane fusion and subsequent viral entry. This work provides a new avenue for the design of anti-SARS therapeutics via strategies aimed at inhibiting viral entry by blocking hairpin formation.

Recently, a third structure has been solved in our laboratory. The complex structure between two non-structural proteins reveals exciting new functional insights into the SARS coronavirus.