



EDUCATION AND POSITIONS HELD:

- B.M., Medicine, National Taiwan University (1968)
- Ph.D., Molecular Biology, University of California, Berkeley (1973)
- Assistant Professor through Distinguished Professor, Dept of Microbiology and Dept. of Neurology, University of Southern California School of Medicine, Los Angeles, California (1973-present)
- Investigator, Howard Hughes Medical Institute (1990-2003)
- Distinguished Research Fellow, Institute of Molecular Biology, Academia Sinica (2003-present)

HONORS:

- Society of Chinese Bioscientists in America-Cathay Hospital Award on Hepatitis Research (1990)
- Academician, Academia Sinica, R.O.C. (1992)
- USC Associates Award for Creativity in Research and Scholarship (1998)
- Fellow, American Academy of Microbiology (2002)
- Taiwanese-American Foundation Science-Technology Achievement Award (2003)
- Honorary Degree in Science, The Central University, Taiwan (2004)

RESEARCH INTERESTS:

**Molecular biology and pathogenesis of RNA viruses**

The primary research interests of our laboratory are the studies of the mechanisms of replication and pathogenesis of several medically important RNA viruses. Our current interest is on three different viruses:

1. Coronavirus: This virus family includes the SARS coronavirus, which causes severe acute respiratory syndrome. This virus contains the largest genome among RNA viruses. Our laboratory has previously performed many pioneering studies on the structure and replication of this virus, particularly viral RNA synthesis. We discovered the phenomenon of high-frequency RNA recombination in this virus. We are focusing on understanding the viral and cellular factors involved in the viral RNA replication. In the immediate future, we will focus on studying the properties of gene products and mechanism of pathogenesis of the SARS coronavirus.

2. Hepatitis C virus (HCV): This virus is one of the most common causes of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Our laboratory is interested in understanding the mechanism of viral RNA replication. Currently we are focusing on studying the structure and mechanism of formation of the viral RNA replication complex. We are also investigating the properties of the various viral gene products in order to identify the potential targets for developing antiviral agents. Finally, my laboratory has developed an in vitro cell culture system for this virus based on the in vivo association of HCV with B-cell lymphoma. This culture system allows for the first time the study of the biology of HCV infection. We have found that HCV infection induces DNA breaks and enhances DNA mutation frequencies, thus explaining the

mechanism of oncogenesis of this RNA virus. We are further exploring the detailed mechanisms of these virus-induced effects.

3. Hepatitis delta virus (HDV): This virus contains a small (1.7 kb) circular RNA genome, which is unique among animal viruses. It replicates by an RNA-dependent RNA replication mechanism, which is carried out by a cellular enzyme. The dilemma is that the mammalian cells do not have RNA-dependent RNA polymerases. It appears that the cellular DNA-dependent polymerase II and possibly other polymerases, together with a unique viral protein hepatitis delta antigen, are involved in this process. This is a novel aspect of cellular machinery. We are further investigating the precise mechanisms of such a process.

### **PEER-REVIEWED PUBLICATIONS**

1. Lai CK, Jeng KS, Machida K, Cheng YS, **Lai MM**. (2008) Hepatitis C virus NS3/4A protein interacts with ATM, impairs DNA repair and enhances sensitivity to ionizing radiation. *Virology*. 370(2):295-309.
2. Aizaki H, Morikawa K, Fukasawa M, Hara H, Inoue Y, Tani H, Saito K, Nishijima M, Hanada K, Matsuura Y, **Lai MM**, Miyamura T, Wakita T, Suzuki T. (2008) Critical role of virion-associated cholesterol and sphingolipid in hepatitis C virus infection. *J Virol*. 82(12):5715-24.
3. Machida K, Kondo Y, Huang JY, Chen YC, Cheng KT, Keck Z, Fong S, Dubuisson J, Sung VM, **Lai MM**. (2008) Hepatitis C virus (HCV)-induced immunoglobulin hypermutation reduces the affinity and neutralizing activities of antibodies against HCV envelope protein. *J Virol*. 82(13):6711-20.
4. Lai CK, Jeng KS, Machida K, **Lai MM**. (2008) Association of hepatitis C virus replication complexes with microtubules and actin filaments is dependent on the interaction of NS3 and NS5A. *J Virol*. 82(17):8838-48.
5. Tseng CH, Jeng KS, **Lai MM**. (2008) Transcription of subgenomic mRNA of hepatitis delta virus requires a modified hepatitis delta antigen that is distinct from antigenomic RNA synthesis. *J Virol*. 82(19):9409-16.
6. Machida K, Tsukamoto H, Mkrtychyan H, Duan L, Dynnyk A, Liu HM, Asahina K, Govindarajan S, Ray R, Ou JH, Seki E, Deshaies R, Miyake K, **Lai MM**. (2009) Toll-like receptor 4 mediates synergism between alcohol and HCV in hepatic oncogenesis involving stem cell marker Nanog. *Proc Natl Acad Sci U S A*. 106(5):1548-53.
7. Kondo Y, Machida K, Liu HM, Ueno Y, Kobayashi K, Wakita T, Shimosegawa T, **Lai MM**. (2009) Hepatitis C virus infection of T cells inhibits proliferation and enhances fas-mediated apoptosis by down-regulating the expression of CD44 splicing variant 6. *J Infect Dis*. 199(5):726-36.
8. Liu HM, Aizaki H, Choi KS, Machida K, Ou JJ, **Lai MM**. (2009) SYNCRIP (synaptotagmin-binding, cytoplasmic RNA-interacting protein) is a host factor involved in hepatitis C virus RNA replication. *Virology*. 386(2):249-56.
9. Hara H, Aizaki H, Matsuda M, Shinkai-Ouchi F, Inoue Y, Murakami K, Shoji I, Kawakami H, Matsuura Y, **Lai MM**, Miyamura T, Wakita T, Suzuki T. (2009) Involvement of creatine kinase B in hepatitis C virus genome replication through interaction with the viral NS4A protein. *J Virol*. 83(10):5137-47.
10. Machida K, Liu JC, McNamara G, Levine A, Duan L, **Lai MM**. (2009) Hepatitis C virus causes uncoupling of mitotic checkpoint and chromosomal polyploidy through the Rb pathway. *J Virol*. 83(23):12590-600.

11. Sung SC, Chao CY, Jeng KS, Yang JY, **Lai MM**. (2009) The 8ab protein of SARS-CoV is a luminal ER membrane-associated protein and induces the activation of ATF6. *Virology*. 387(2):402-13.
12. Tseng CH, Cheng TS, Shu CY, Jeng KS, **Lai MM**. (2010) SUMO modification of small hepatitis delta antigen. *J Virol*. 84(2):918-27.
13. Chen YC, Su WC, Huang JY, Chao TC, Jeng KS, Machida K, **Lai MM**. (2010) Polo-like kinase 1 is involved in hepatitis C virus replication by hyperphosphorylating NS5A. *J Virol*. 84(16):7983-93.
14. Machida K, Tsukamoto H, Liu JC, Han YP, Govindarajan S, **Lai MM**, Akira S, Ou JH. (2010) c-Jun mediates hepatitis C virus hepatocarcinogenesis through signal transducer and activator of transcription 3 and nitric oxide-dependent impairment of oxidative DNA repair. *Hepatology*. 52(2):480-92.
15. Machida K, McNamara G, Cheng KT, Huang J, Wang CH, Comai L, Ou JH, **Lai MM**. (2010) Hepatitis C virus inhibits DNA damage repair through reactive oxygen and nitrogen species and by interfering with the ATM-NBS1/Mre11/Rad50 DNA repair pathway in monocytes and hepatocytes. *J Immunol*. 185(11):6985-98.
16. Su CY, Cheng TJ, Lin MI, Wang SY, Huang WI, Lin-Chu SY, Chen YH, Wu CY, **Lai MM**, Cheng WC, Wu YT, Tsai MD, Cheng YS, Wong CH. (2010) High-throughput identification of compounds targeting influenza RNA-dependent RNA polymerase activity. *Proc Natl Acad Sci U S A*. 107(45):19151-6.
17. Lai CK, Jeng KS, Machida K, **Lai MM**. (2010) Hepatitis C virus egress and release depends on endosomal trafficking of core protein. *J Virol*. 84:11590-8.
18. Liao TL, Wu CY, Su WC, Jeng KS and **Lai MM**. (2010) Ubiquitination and deubiquitination of NP protein regulates influenza A virus RNA replication. *The EMBO Journal* 29:3879-90.
19. Wu CY, Jeng KS, **Lai MM**. (2011) The SUMOylation of Matrix Protein M1 Modulates the Assembly and Morphogenesis of Influenza A Virus. *J Virol*. 85:6618-28.
20. Wang L, Jeng KS, **Lai MM**. (2011) Poly(C)-binding protein 2 Interacts with sequences Required for Viral Replication in HCV 5' UTR and Directs HCV RNA Replication through Circularizing the Viral Genome. *J Virol*. 85:7954-64.
21. Su WC, Chao TC, Huang YL, Weng SC, Jeng KS, **Lai, MM**. (2011) Rab5 and Class III Phosphoinositide 3-Kinase Vps34 Are Involved in Hepatitis C Virus NS4B-Induced Autophagy. *J Virol*. 2011 85:10561-71.