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MAJOR RESEARCH INTERESTS

Currently, the two main research focuses in my laboratory involve different degrees of interdisciplinary aspects of Statistical, Computational Analyses, as well as Cell and Molecular Genetics. My research group collaborates both locally with medical doctors, surgeons, scientists, statisticians and engineers as well as internationally:

1) *Functional Genomics of Hepatocellular Carcinoma*

Hepatocellular carcinoma (HCC) is amongst the commonest cancers which occur in a background of chronic inflammation. However, the molecular and cellular mechanisms of inflammation-induced tumorigenesis remains incompletely understood. We previously found that FAT10 is over-expressed in the tumors of HCC patients and its expression is cell-cycle regulated and negatively-regulated by p53. We demonstrated that FAT10 which can be induced by Tumor Necrosis Factor-alpha (TNFα) and gamma-interferon (IFNγ) interacts with the spindle checkpoint protein, MAD2, during the mitotic phase of the cell-cycle and high levels of FAT10 protein leads to increased mitotic non-dysjunction and chromosome instability (CIN) and tumorigenesis. Recently, together with our collaborators, we determined the NMR structure of FAT10 and identified residues within FAT10 that is important for its interaction with MAD2. We then showed that genetic abrogation of the FAT10–MAD2 interaction restored daughter cells to having normal chromosome numbers and curtailed tumor progression without affecting FAT10's interaction with its other known physiological binding partners. This study presents a paradigm for drug targeting and paves the way for the development of a novel small-molecule anticancer inhibitor targeting the MAD2-binding interface of FAT10.

Our laboratory is also interested in the role of Hepatitis B Virus in HCC and had employed next-generation sequencing to comprehensively characterize HBV in HCC patients. Among the four proteins translated from the HBV genome, the X-gene product (HBx) has been implicated in hepatocarcinogenesis. Our strategy is to utilize a combination of bioinformatics as well as molecular and cellular biological techniques including cDNA microarrays, microRNA (miRNA) microarrays, chromatin-immunoprecipitation (ChIP) arrays, confocal microscopy, flow cytometry, etc to identify and characterize genes / miRNAs that may play a role in the hepatocarcinogenesis process and the role that the HBx protein may play in this process.

2) *Population Genetics of Polymorphisms in Drug Response Genes*

The ultimate goal is to usher in the era of personalized medicine in which medication can be tailored according to the individual's genetic profile. With the completion of the Human Genome Project as well as the identification of >10 million polymorphisms that may potentially account for differences between individuals, the daunting task ahead is to sieve through these polymorphisms to identify potentially functional ones that may be used to distinguish differences in drug response, etc. Our strategy is to utilize statistical genetics / computational approaches to identify these potentially functional polymorphisms through their signatures of recent positive selection. We then utilize molecular and cellular approaches to validate the functionality of these polymorphisms in vitro before we validate them in vivo through performing association studies on patients' samples. Drugs approved

for use here in Singapore and elsewhere are often only tested on a particular (e.g. Caucasian) population in another country (usually USA). However, due to genetic differences, different ethnic groups often respond differently to the same drugs. Integrating the potential functional SNP resource that our laboratory has developed, gene-pathway information as well as algorithms for predicting population differences, we aim to develop robust algorithms to identify drugs/drug groups there are significant population differences in the pharmacokinetic as well as pharmacodynamic pathways for that particular drug/drug group. The algorithm aims to also be able to advice the doctors the potentially functional SNP(s) that may potentially influence drug response that are significantly different between their population and the clinical-trial tested population.

RECENT REPRESENTATIVE PUBLICATIONS (out of ~100)

1. Yu WANG, Yiwei LU, Soo Ting TOH, Wing-Kin SUNG, Patrick TAN, Pierce CHOW, Alexander YF CHUNG, London L. P. J OOI and **Caroline G.L. LEE***. Lethal-7 is down-regulated by the Hepatitis B virus x protein and targets Signal Transducer and Activator of Transcription 3. **Journal of Hepatology** 53: 57–66 (2010).
2. Jingbo Wang, Mostafa Ronaghi, Samuel S Chong, **Caroline GL Lee***. pfSNP: An Integrated Potentially Functional SNP Resource that facilitates Hypotheses Generation through Knowledge Syntheses. **Human Mutation** 32(1):19-24 (2011).
    a. Cited as one of the useful meta tools by UK Gen2Phen biomedical knowledge center community
    b. Cited as a useful tool for "Candidate SNP selection and SNP annotation" by GenEpi Toolbox
3. Jianwei Ren, Yu Wang, Yun Gao, Shalin BK Mehta and **Caroline GL Lee***. FAT10 mediates the effect of TNF-α in inducing chromosomal instability. **Journal of Cell Science** 124, 3665–3675 (2011)
    a. Selected for inclusion in the 'In This Issue' section of the **Journal of Cell Science** 124:e2105.
4. Yu WANG, Han Chong TOH, Pierce Chow, Alexander YF Chung, David Meyers, Philip A. Cole, London L. P. J Ooi, **Caroline G.L. LEE***. MicroRNA-224 is Up-regulated in Hepatocellular Carcinoma through Epigenetic Mechanisms. ***FASEB J*** 26(7): 3032-3041 (2012)
5. Cheryl CHAN, Yu WANG, Pierce K.H. CHOW, Alexander Y.F. CHUNG, London L.P.J. OOI, and **Caroline G. LEE***. Altered Binding Site Selection of P53 Transcription Cassettes by Hepatitis B Virus X Protein. ***Molecular and Cellular Biology*** 33(3):485-497 (2013).
6. Soo Ting Toh, Yu Jin, Lizhen Liu, Jingbo Wang, Farbod Babrzadeh , Baback Gharizadeh, Mostafa Ronaghi, Han Chong Toh, Pierce Kah-Hoe Chow , Alexander Y-F Chung, London L.-P- J Ooi, **Caroline G-L Lee***. Deep sequencing of the Hepatitis B Virus in Hepatocellular Carcinoma patients reveals enriched integration events, structural alterations and sequence variations. ***Carcinogenesis*** 34(4): 787–798 (2013)
7. Yun Gao, Steven Setiawan Theng, Jingli Zhuo, Wei Bing Teo, Jianwei Ren and **Caroline G.L. Lee***. FAT10, an Ubiquitin-like Protein, Confers Malignant Properties in Non-tumorigenic and Tumorigenic Cells. **Carcinogenesis**. 2014 Apr;35(4):923-34.
8. Way-Champ MAH, Thomas THURNHERR, Pierce KH CHOW, Alexander YF CHUNG, London LPJ OOI, Han Chong TOH, Bin Tean TEH, Yogen SAUNTHARARAJAH and **Caroline G.L. LEE*.** Methylation Profiles Reveal Distinct Subgroup of Hepatocellular Carcinoma Patients with Poor Prognosis. **PLoS One** 9(8): e104158 (2014). doi:10.1371/journal.pone.0104158
9. Jingbo WANG, Xu WANG, Mingjue ZHAO, Su Pin CHOO, Sin Jen ONG, Simon YK ONG, Samuel S CHONG, Yik Ying TEO, **Caroline GL LEE***. Potentially Functional SNPs (pfSNPs) as Novel Genomic Predictors of 5-FU Response in Metastatic Colorectal Cancer Patient. **PLoS One** 9(11): e111694 (2014)
10. Betty L. Slagle, Ourania M. Andrisani, Michael J. Bouchard, **Caroline G. L. Lee**, J.-H. James Ou, and Aleem Siddiqui. Technical Standards for Hepatitis B Virus X protein (HBx) Research. **Hepatology** Aug 7. doi: 10.1002/hep.27360 (2014)
11. Steven Setiawan Theng, Wei Wang, Way Champ Mah, Cheryl Chan, Jingli Zhuo, Yun Gao, Haina Qin, Liangzhong Lim, Samuel S. Chong, Jianxing Song and **Caroline G.L. Lee***. Disruption of FAT10-MAD2 binding inhibits Tumor Progression **PNAS** 111(49):E5282-5291 (2014)
12. Ling Li, David Ng, Way-Champ Mah, Francisca Almeida, Siti Aishah Rahmat, Vinay Kumar Rao, Shi Chi Leow, Federica Laudisi, Meng Teng Peh, Amanda Goh, John Lim, Graham Wright, Alessandra Mortellaro, Reshma Taneja, Florent Ginhoux, **Caroline Lee**, Philip K Moore, and David Lane. A unique role for p53 in the regulation of M2 macrophage polarization. **Cell Death and Differentiation** (accepted).

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