

**NUS Graduate School for Integrative Sciences and Engineering  
Research Project Write-up**

**Title of Project :** Elucidation of gene regulation mechanism in Cyr61 to understand the downregulation of its expression in hepatocellular carcinoma.

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**Short Description**

Hepatocellular carcinoma (HCC) is a one of the most prevalent cancers worldwide, especially in the Asia Pacific region. At present, the five-year survival of individuals with HCC is low, mainly due to the late presentation of the disease, and limited therapeutic options. Current treatment strategies include surgical resection, liver transplantation, chemotherapy, transcatheter arterial chemoembolism and percutaneous injection. Except for surgical resection and liver transplantation, which represent the most viable treatment options, most of the other present treatments are mainly for palliation. Hence novel treatment modalities have to be explored. In the climate of post-genomics and bioinformatics, we are poised to discover better biological therapies and new tumour targets. Through cDNA microarray analyses of a few HCC patients, we identified Cyr61 as a gene that is consistently down-regulated in the tumors of HCC patients. To facilitate the design of therapeutic strategies targeting this gene, an understanding of the gene regulation of Cyr61 and its dysregulation during carcinogenesis is necessary. Hence in this grant, we propose to elucidate the mechanism of regulation of the Cyr61 gene and its dysregulation during hepatocellular carcinogenesis.

There are two interesting features about the Cyr61 promoter. Firstly, it contains two long stretches of repeats, each comprising d(CA) dinucleotide repeats downstream of HNF3 $\beta$  and ATF binding sites. Secondly, the Cyr61 promoter is CG-rich containing at least 49 CGs within a region of approximately 1 kb. In this project, we would like to test the hypothesis that either the variability of dinucleotide repeats or mutations within the promoter region or variability in epigenetic events or differentially availability of factors binding to the Cyr61 promoter differentially regulate expression of the Cyr61 promoter in tumor versus adjacent normal tissues in HCC patients resulting in dysregulation of the Cyr61 promoter during HCC carcinogenesis. This study should facilitate the understanding of gene regulation in general as well as its dysregulation during tumorigenesis.

**Objectives**

- (1) Screen for mutations at the Cyr61 promoter region in the tumors of HCC patients and evaluate if these mutations can account for the down-regulation of the Cyr61 promoter in HCC patients.
- (2) Screen for differential epigenetic events (i.e. methylation) in the tumor versus normal liver tissues to evaluate if these epigenetic events might account for the down-regulation of the Cyr61 promoter in HCC patients.
- (3) Screen for differential availability of factors binding to the Cyr61 promoter in the tumor versus normal liver tissues to evaluate if these differential binding of factors to Cyr61 promoter might account for the down-regulation of the Cyr61 promoter in HCC patients.

**References**

- 1) Baoshuang Wang, Jianwei Ren, London L.P.J Ooi, Samuel S. Chong, **Caroline.GL. Lee\***. Dinucleotide Repeats Negatively Modulate Promoter Activity of Cyr61 and is Unstable in Hepatocellular Carcinoma patients. *Oncogene* 24(24): 3999-4008 (2005)