Functional characterization of the US12 gene family of Human Cytomegalovirus

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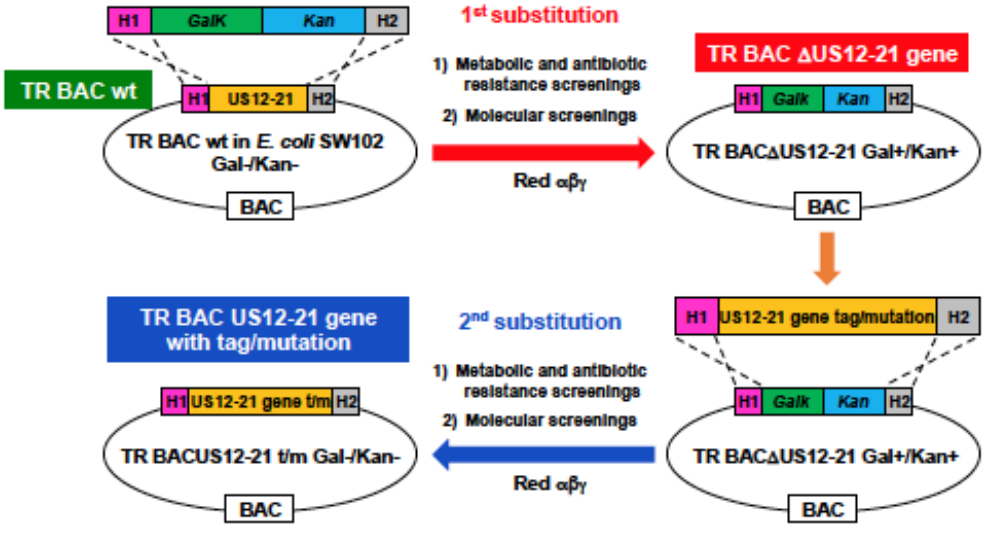
Human Cytomegalovirus (HCMV) is a widespread opportunistic viral pathogen that establishes a lifelong persistence in the host through both chronic and latent infections. HCMV causes life-threatening diseases in immunologically compromised individuals, such as transplant recipients and AIDS patients, for whom prolonged antiviral therapies are necessary. HCMV is also the major viral cause of congenital infections that lead to developmental abnormalities and fetal death (1-3). Nevertheless, to date, no vaccine is available to prevent HCMV infection and only a limited number of drugs all targeting the viral DNA polymerase are licensed to manage HCMV diseases. However, their clinical utility is limited by several drawbacks and no drugs have been yet approved for treatment of congenital HCMV infections. Given this, there is an urgent need to develop new, safe, and effective anti-HCMV compounds, possibly endowed with alternative mechanisms of action to avoid cross-resistance and decrease the risk of selection of resistant strains. Therefore, the identification and characterization of other HCMV proteins as virus-specific druggable targets is an essential step to design and develop new pharmacological strategies.

To this end, using a systematic reverse genetics approach by BAC-recombineering of the HCMV genome (summarized in the figure), we investigate the functional role of the US12 gene family of HCMV in the context of the viral replication in cell types relevant for viral pathogenesis, such as endothelial cells and epithelial cells. The US12 gene family is a set of 10 contiguous genes (US12 to US21) that constitutes about 5% of HCMV's genetic content and predicted to encode membrane-associated seven-transmembrane (7TMD) proteins. During my PhD, we have observed that: a) some US12 family members contribute to the HCMV cell tropism for specific cell types, as demonstrated by inactivation of US16, US18, US20, and US21 family members that abrogates virus growth in endothelial and epithelial cells; b) the US16 protein is required to regulate the entry of HCMV virions in these cell types (4); and c) the US20 protein is important in endothelial cells and regulates the composition of viral particles in a way as to influence a post-entry phase of the virus replication cycle in this cell type (5). Together, these findings characterize novel HCMV proteins as important factors for viral pathogenesis and whose functions could be exploited to design novel anti-HCMV intervention strategies.



Manipulation of HCMV US12-21 gene family by BAC recombineering

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