**Human Cytomegalovirus and Drug interaction**

**Abstract:** Human cytomegalovirus (HCMV) infection is the leading infectious cause of congenital disorders in newborns. Congenital HCMV infection causes permanent neurological and neurocognitive disabilities and results in significant health problems worldwide(1-5) . No vaccine is available. The drugs currently used against CMV are either the synthetic acyclic analogue of 2′-deoxy-[guanosine](https://en.wikipedia.org/wiki/Guanosine) and its derivatives targeting viral DNA replication or small compounds targeting the CMV terminase complex(6-8). Drug resistances frequently occur and none of them can be used for foetal exposure(9-11). A novel and specific interference with viral replication is needed against CMV infection, especially congenital CMV infection. Our **long-term goal** is to develop specific anti-CMV drugs that can be harmlessly exposed to fetuses via understanding how CMV interferes with stem cell development. Our preliminary results demonstrated that HNT-1 drug inhibits HCMV growth in the invitro and invivo condition. More specifically, HNT-1 drug completely inhibits HCMV infection at 10nM concentration. Using skin fetus tissues, we demonstrated that replication and growth of the HCMV is completely inhibited by HNT drug. Using HCMV-GFP virus, we demonstrated that HNT does not allow the virus replication by unknown mechanism. Moreover, using mouse cytomegalovirus, we demonstrated that HNT-1 treated MCMV cannot replicates in the mouse and generate robust immune response sufficient to clear the new infection.

**Objectives**

**Aim 1: To examine molecular mechanisms of HNT-1 drug effect on the HCMV via cryo-electron microscopy.**

**Aim 2: To synthesize more specific and potent chemical variants of HNT-1 drug based on the structure-function analysis obtained in the aim 2.**

Based on the results obtained in the preliminary study, we would like to determine HCMV structure in presence of HNT-1 drug to elucidate the molecular mechanism of HNT-1 drug action on the virus. This study will help to design new potent inhibitors based on the structure of virus. We believe that the present proposal by **multiple principle investigators** is **innovative** and should be given an opportunity. In our study, we are using AD169 strain of HCMV which has been evaluated as a live attenuated virus in clinic (Elek and Stern, 1974; Neff et al, 1979), and the results clearly demonstrated that the virus can’t cause any active infection in human subjects, with no pathology (symptom) or viral shedding when dosed even at 300,000 pfu. Therefore, it is safe to work with this strain of the HCMV.

**Significance**

Congenital human cytomegalovirus (HCMV) infection resulting in brain defects and intellectual disability remains a major medical and public health issue.CMV is the most common congenital viral infection, affecting up to 1% of infants. Congenital HCMV infection is the most common intrauterine infection in the United States today(3). Of the estimated 4 million births annually in the United States, approximately one percent of these babies are born with a congenital CMV infection. About ten percent of congenitally infected babies have symptoms at birth, and many will suffer some kind of permanent disability(3). The remaining ninety percent of congenitally infected babies are asymptomatic and appear normal at birth. However, up to fifteen percent of these infants who appear symptom-free at birth have permanent disabilities later in life(12-14). Both symptomatic and asymptomatic infants may later develop sequelae. Sequelae following congenital CMV infection include sensorineural hearing loss (SNHL), retinitis, mental retardation, intellectual disability, microcephaly, seizures, and cerebral palsy(15). In the United Sates, the incidence of long-term problems resulting from congenital CMV infection is greater than those combined of fetal alcohol syndrome, Down syndrome, and neural tube defects(16). No vaccine or therapy regimens are available for the treatment of congenital CMV diseases; therefore, the new drugs are imminently needed and understanding of the pathogenic mechanism is important for developing specific anti-CMV strategies(10).

**Neurogenesis and neurodevelopmental disorders and CMV infection.** Although HCMV can infect multiple organs, the most severe and permanent disorders caused by congenital HCMV infection are those affecting the cerebrum, such as microcephaly, epilepsy, and mental retardation(17). These sequelae are found more frequently in infants infected during the first trimester, a critical period for cerebral corticogenesis, than in those infected during the later trimesters(18).

**Scientific Feasibility \***

Although Zhu lab at NJMS is not a structural biology lab, but to complement our expertise, we are collaborating with the Dr. Appu Singh, a faculty in BSBE, IIT Kanpur, who has demonstrated strong and terrific scientific capability to determine the structures of TRP channels. In collaboration with him, we will determine the HCMV virion structure in the presence of HNT-1 that will determine target of drug, and suggest feasibility of our research goals.

**Resources Requested \***

Cryo EM training

**Geographic/Demographics \***

Currently, there is no high-end cryo-EM microscope at NJMS, and therefore, we solely rely on the national facility like NYSBC for our need of cryo-EM. Our projects are highly competitive and therefore, being competitive, we require these cryo-EM time at NYSBC to facilitate our research and develop molecular model of temperature activation of TRP channels.

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