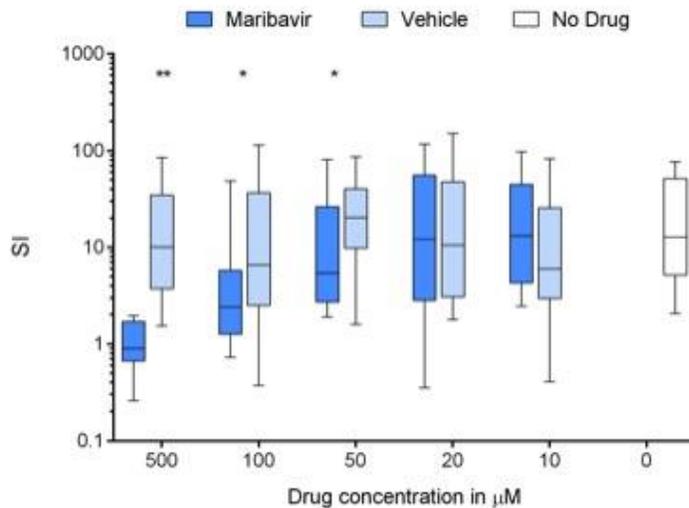


Aim at the target: cytomegalovirus

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CD4+ lymphoproliferative responses to CMV as measured by carboxyfluorescein succinimidyl ester (CFSE) assay. * $p < 0.05$, ** $p < 0.01$ by Wilcoxon signed-rank test. Whiskers represent minimum and maximum. Concentrations below 10 μM not shown.

Image provided by Terry Stevens-Ayers.

Cytomegalovirus (CMV) is a common infectious agent that rarely causes symptoms. However, it can be a reason of concern if the infections happen in particular circumstances, such as during pregnancy, when it can endanger the fetus, or in situations characterized by a weakened immune system, such as during hematopoietic stem cell or solid organ transplantation. Although neither a cure nor vaccine against CMV is available yet, some drugs can control viral replication and prevent disease progression. The drugs brought to clinic so far belong to the nucleoside-analogue family. Although such compounds target CMV replication, they also inhibit DNA synthesis in mammalian cells, therefore affecting highly proliferating cell populations such as those of the immune system. This side effect is particularly relevant after transplantation, since it might inhibit the reconstitution of the immune compartment, therefore increasing the possibility of infections. Maribavir, an experimental oral antiviral drug candidate for the prevention and treatment of human CMV disease in hematopoietic stem cell transplant patients, works by inhibiting a CMV-encoded protein kinase called UL97, an enzyme involved in viral nuclear egress. Maribavir showed promise in a phase II clinical trial, but failed to meet study goals in a phase III trial. However, questions arose whether the dosage used in the phase III trial may have been too low to be efficacious. The effect of maribavir on the reconstitution of CMV-specific immune responses has not been evaluated.

A study performed by Dr. Daniel Stachel and Terry Stevens-Ayers from the Boeckh Laboratory (Vaccine and Infectious Disease Division) evaluated the effects of maribavir on immune cell function in response to stimulation with whole viral lysate or specific CMV peptides. The results were published recently in the *Journal of Clinical Virology*.

The study used blood from healthy CMV-seropositive donors to investigate the in vitro effects of a range of maribavir and ganciclovir concentrations on cell proliferation, cytokine production, cellular degranulation and lymphocyte apoptosis (a physiological type of cell death) in response to CMV proteins. Maribavir concentrations equal or above 50µM reduced CMV-specific proliferation of total peripheral blood mononuclear cells, while the same effect was observed for ganciclovir at lower concentrations. The frequencies of CMV-specific CD4+ and CD8+ T cells that expressed cytokines or degranulated were not affected by either drug, aside from CD4+ T cells exposed to 500µM maribavir. Finally, CD4+ and CD8+ T cell apoptosis was not affected by the drugs.

"Our data suggest that maribavir inhibits CMV-specific cellular immune function less than ganciclovir at clinically relevant doses. This finding may support clinical prophylaxis studies of maribavir using higher doses", said Dr. Stachel, re-opening the opportunity of using this CMV-targeting drug in the transplant setting, where the reconstitution of the immune system and associated proliferation of its cellular components is vital for recovery.

The study was supported by Viropharma, Inc.

[Stachel D, Stevens-Ayers T, Boeckh M.](#) 2015. In vitro studies of the impact of maribavir on CMV-specific cellular immune responses. *J Clin Virol.* 75: 53-59.