Genotoxic Potential of an Antiviral Pyrimidine Nucleoside Analogue, 5-(2-chloroethyl)-2′-deoxyuridine (CEDU)

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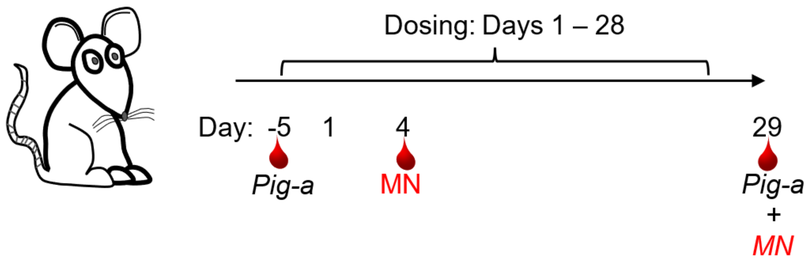
ABSTRACT

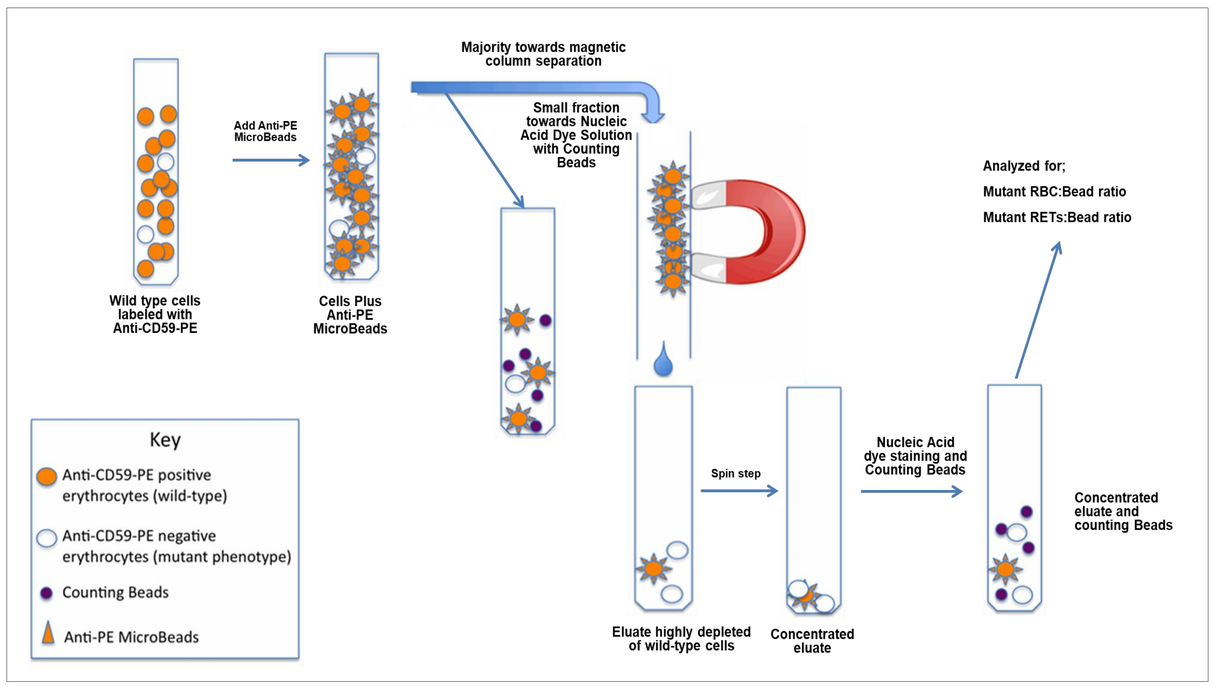
- 5-(2-Chloroethyl)-2'-deoxyuridine (CEDU) is a nucleoside analogue developed as an antiviral drug by Novartis. In studies conducted by Novartis, CEDU was evaluated negative in an in vitro and in vivo micronucleus assay, but positive in Ames assay, *Pig-a* assay, and Transgenic Rodent Assay using MutaMouse®.
- Given the unusual and interesting genotoxic profile CEDU, an in vivo study was conducted with CEDU to further investigate its genotoxic potential. In this study, male and female Sprague-Dawley rats were administered CEDU at dose levels of 30, 100, 300, and 1000 mg/kg/day for 28 consecutive days. Blood was collected on Days -5 and 29 to conduct the *Pig-a* assay and Days 4 and 29 to conduct peripheral blood micronucleus assay.
- No increase in peripheral blood micronucleated reticulocytes frequency (%MN-RETs) was observed at any tested dose levels either on Days 4 or 29. However, a statistically significant increase in mutant reticulocytes (Mut-RETs) and mutant red blood cells (Mut-RBCs) frequencies was observed at all tested concentrations in males and females except 30 mg/kg/day where mean Mut-RBCs frequency in males was not statistically significant compared to the control. A dose related increase was observed in both males and females in Mut-RBCs and Mut-RETs. Multiple tissues from treated animals were collected on Day 29 and were flash frozen for future error corrected Next Generation Sequencing (ecNGS analysis).
- The data indicate that CEDU has mutagenic potential as demonstrated by a clear increase in the *Pig-a* mutant RBCs and RETs frequencies while no clastogenic effects as demonstrated by the negative response in the micronucleus assay.

INTRODUCTION

5-(2-chloroethyl)-2'-deoxyuridine (CEDU) is a nucleoside analogue. It was developed for the treatment of herpes simplex infections. It is a potent inhibitor to stop proliferation of herpes simplex virus type 1 (HSV-1) by inhibiting viral DNA polymerase and cellular DNA polymerase alpha. CEDU has been evaluated in a number of genotoxicity assays. It has previously been tested in a number of in vitro and in vivo genotoxicity assays. CEDU has been tested negative for clastogenicity/aneugenicity in the in vitro micronucleus (MN) assay using V79 cell line and bone marrow MN assay in CD1 mice. It has been tested positive in Ames assay (at higher conc), transgenic rodent assay and *Pig-a* assay in males. In this study, CEDU was first time tested in female rats for a direct comparison of males and females at doses ranging from very low (30 mg/kg/day) to limit dose (1000 mg/kg/day) with consecutive 28 days of dosing.

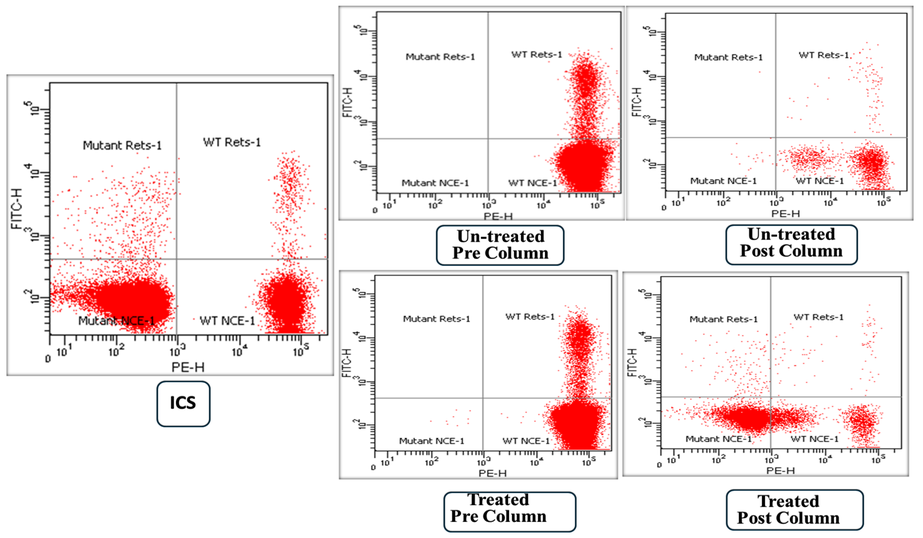
METHODOLOGY





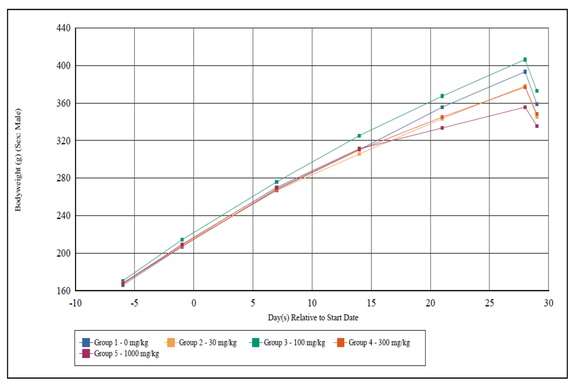
Dertinger et al., 2011; Mutat Res. 721: 163–170

METHODOLOGY (CONT)

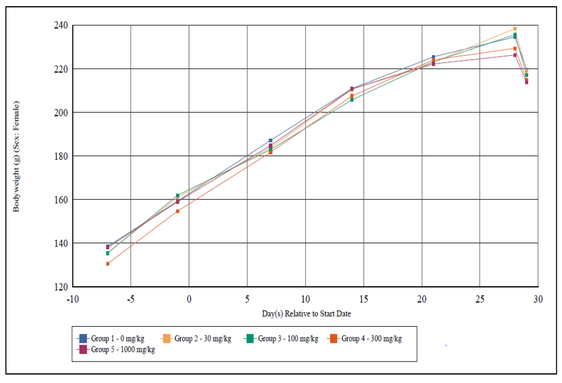


RESULTS

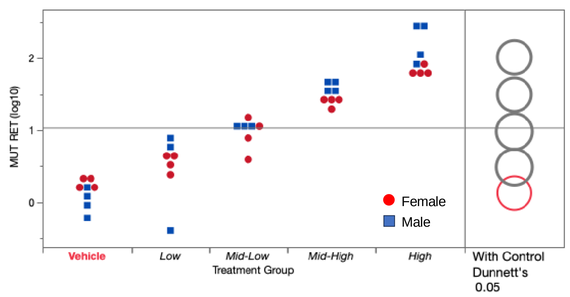
Effect of CEDU Treatment on Body Weight (Males)



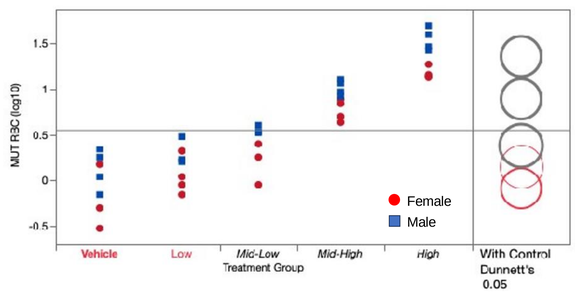
Effect of CEDU Treatment on Body Weight (Females)



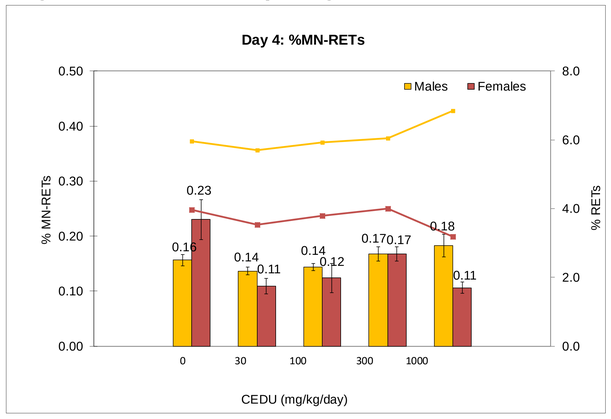
Day 29: Sex Combined One Way Analysis of MUT RET (Log_{10}) By Treatment Group



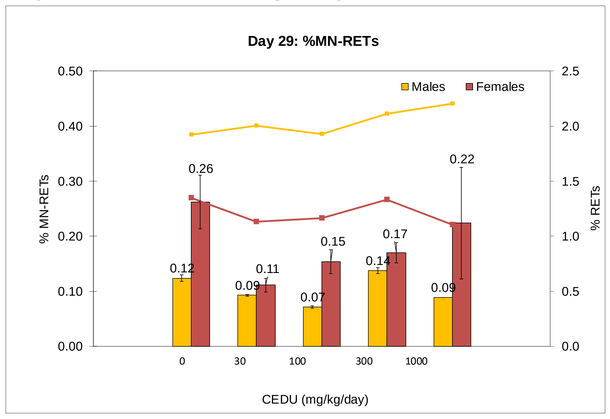
Day 29: Sex Combined One Way Analysis of MUT RBC (Log_{10}) By Treatment Group



Day 4: %MN-RETs Frequency in Males and Females



Day 29: %MN-RETs Frequency in Males and Females



CONCLUSION

5-(2-chloroethyl)-2'-deoxyuridine (CEDU) was tested positive in the *Pig-a* assay and negative in the rat micronucleus assay indicating that it causes genotoxicity through mutagenic mode of action and not through clastogenicity or aneugenicity.