

PROGRAM #
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Abstract #
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Immunotherapy of Acute Leukemia with Cationic Lipid DNA Complexes (JVRS-100)

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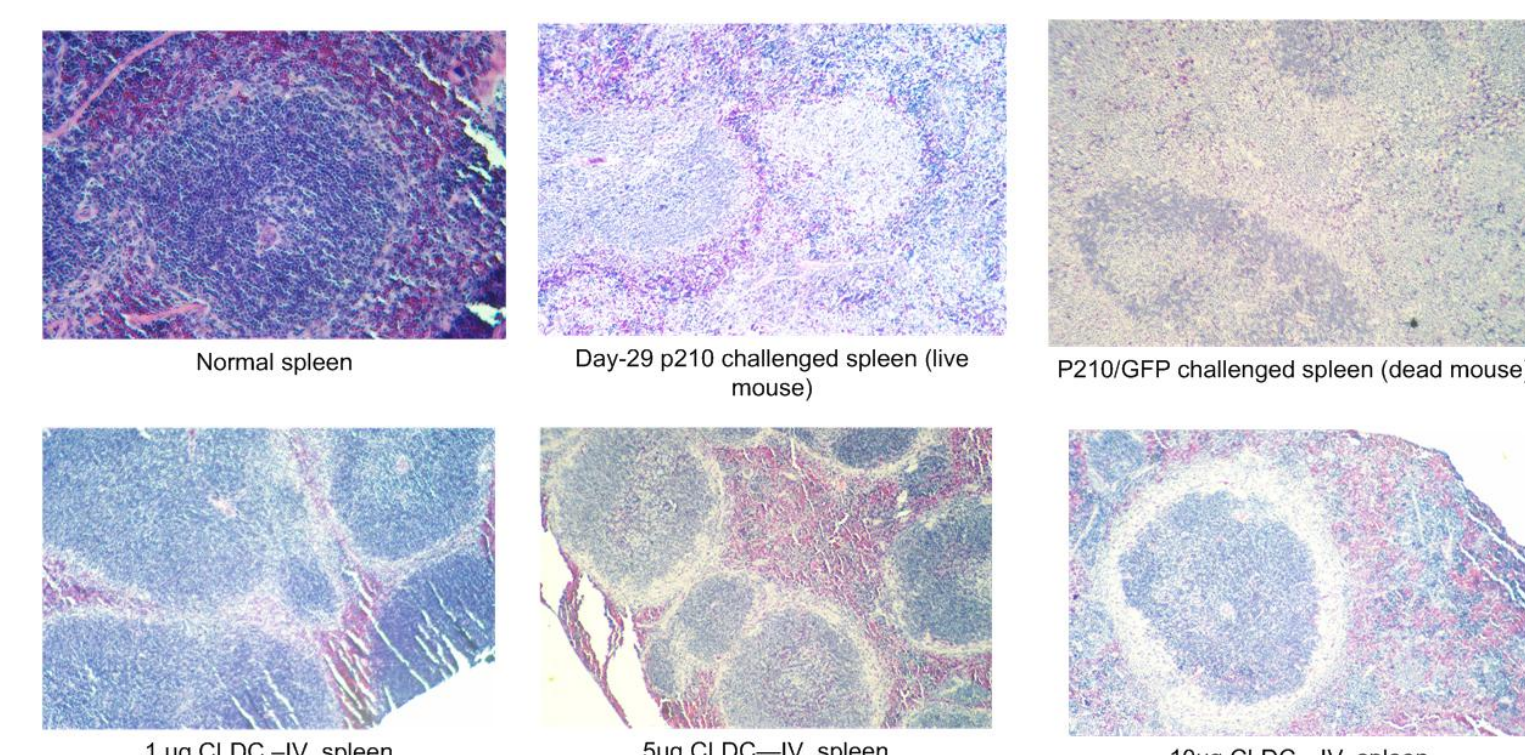
INTRODUCTION

Acute leukemias have long been recognized as suitable targets for immunotherapy. Administration of cationic liposome-DNA complexes (JVRS-100) elicits cytokines of the T_H1 subset, especially IL-12, IFN-gamma and IFN-alpha. These cytokines are particularly important in mediating host defense against cancer. In multiple experiments using the 32Dp210-GFP model, intravenous dosing of JVRS-100 prevented or significantly delayed death from leukemia when delivered between 7 and 15 days following leukemic challenge. Specifically, control animals died at ~19 days of leukemia whereas 80% of similarly leukemia challenged but JVRS-100 treated animals (1 ug) were alive >40 days with weekly treatment beginning at day 15 (4 days prior to expected mortality). Animals dying of leukemia had splenomegaly and leukemic infiltration of spleen and liver. The GFP expression allowed quantification of leukemia in peripheral blood (PB). At day 12 following challenge PB leukocytes were ~30% GFP positive with either no treatment, or 0.1 ug JVRS-100, <0.1% with 1.0 ug or 5.0 ug JVRS-100 treatment at days 2 and 9. Furthermore there is a similar cell activation profile and cytokine response *in vitro* following exposure of human PBMCs to JVRS-100 as is observed following *in vivo* administration of JVRS-100 to mice, making this immunostimulation technology a promising candidate for product development and eventual clinical evaluation.

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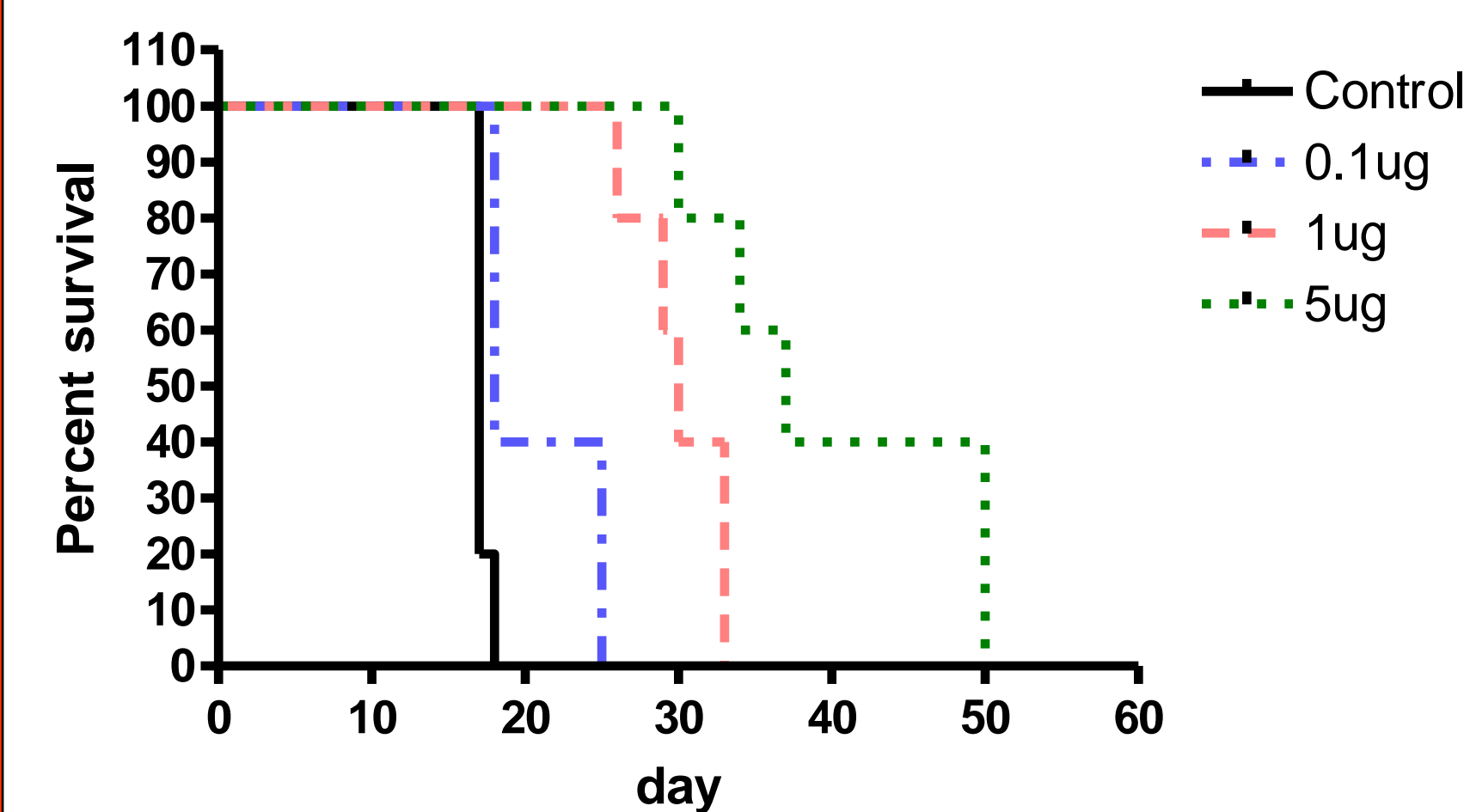
RESULTS

Histology Following Leukemia Challenge or JVRS-100 (CLDC) Treatment (no challenge)



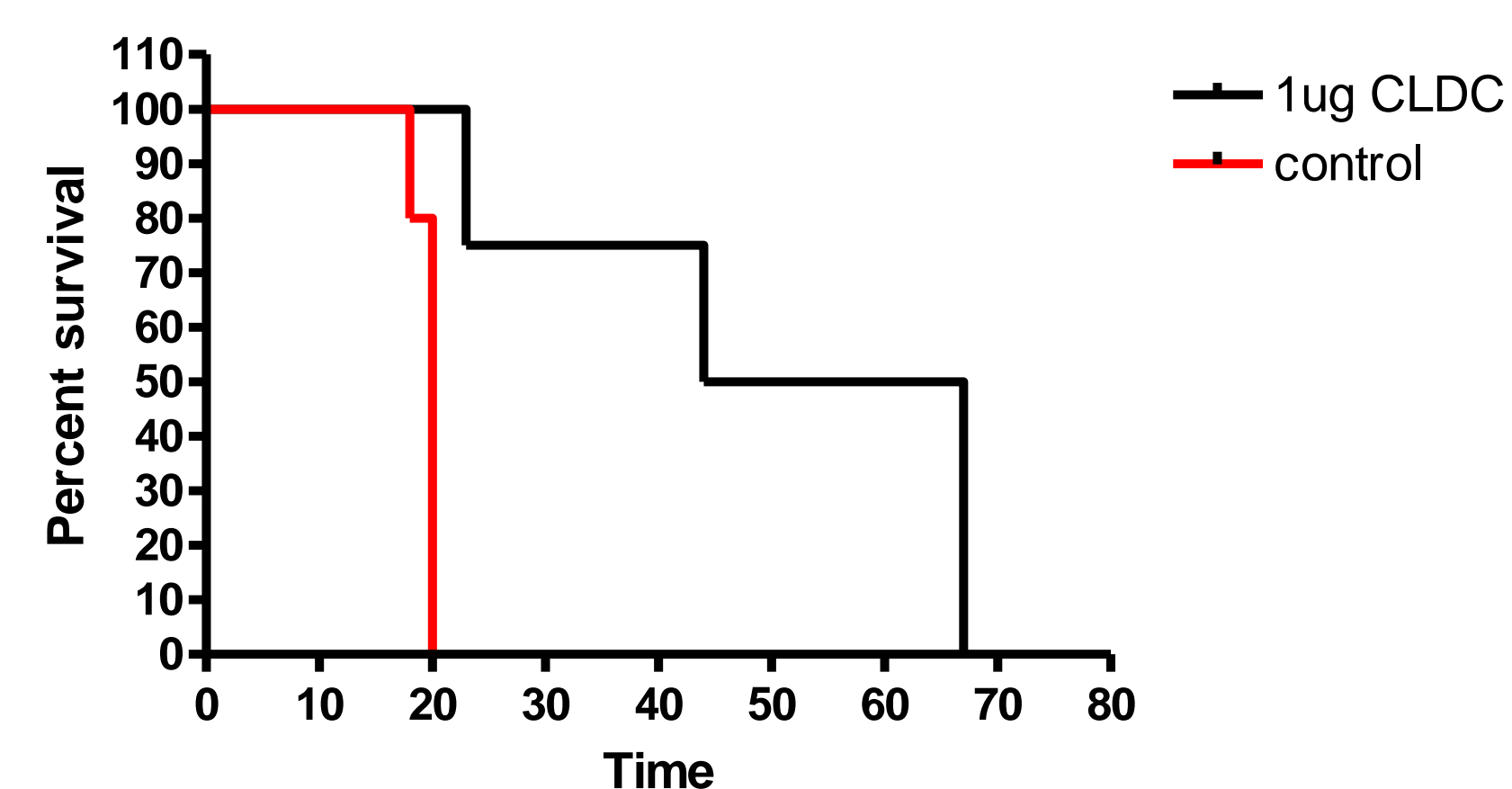
Shown above is H&E staining of spleens from mice challenged with 32D/BA (upper panel) or treated with JVRS-100 without challenge (lower panel). Note the enlarged splenic marginal zones in the JVRS-100 treated animals

Dose Dependent Survival Benefit of JVRS-100 (CLDC) Treatment



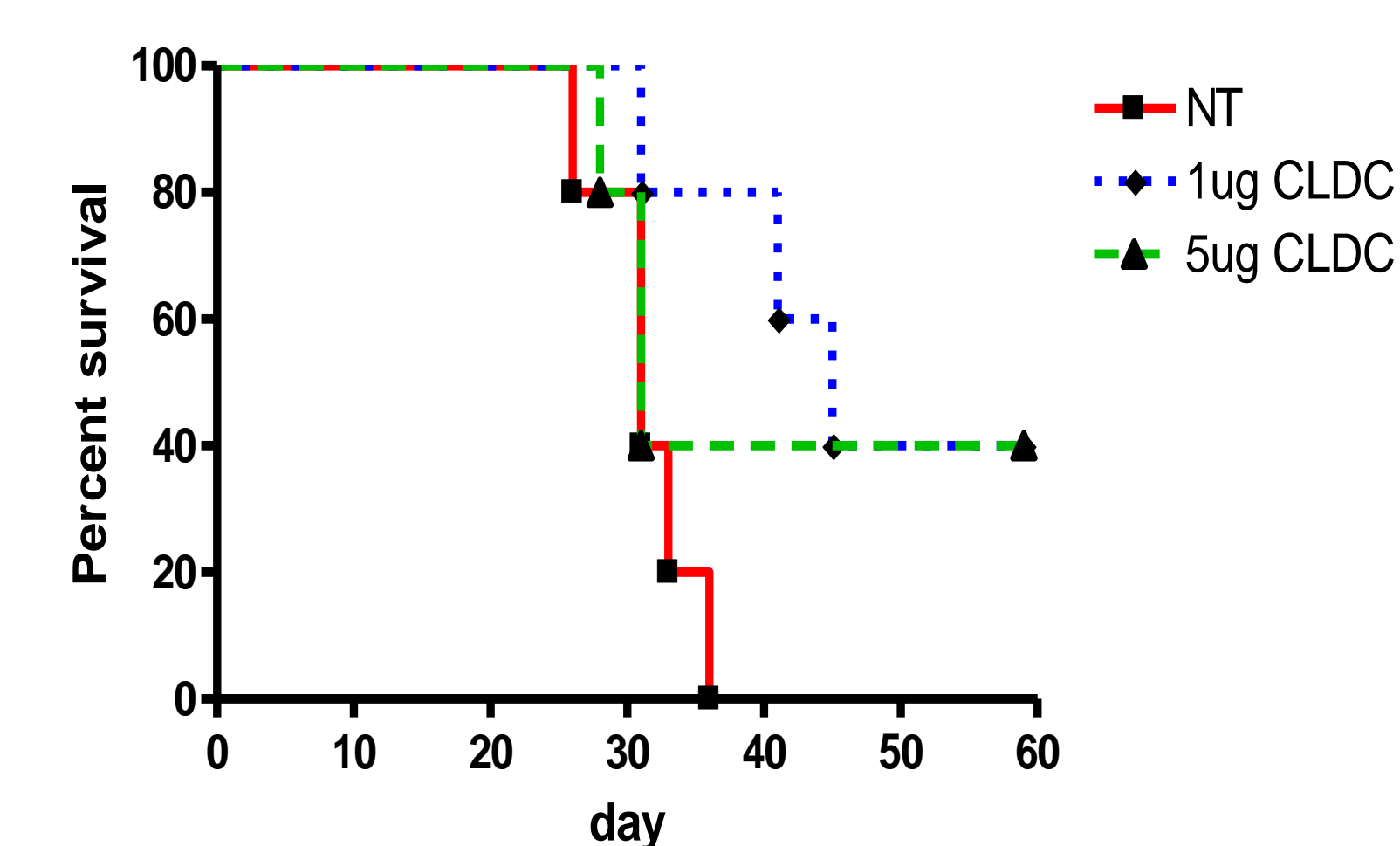
Animals received IV JVRS-100 at doses of 0.1ug, 1ug, and 5ug day 2 and 9 following 32D/BA-GFP challenge. Survival benefit was observed in a dose dependent relationship.

Survival Following Low-Dose IV Therapy with JVRS-100 (CLDC)



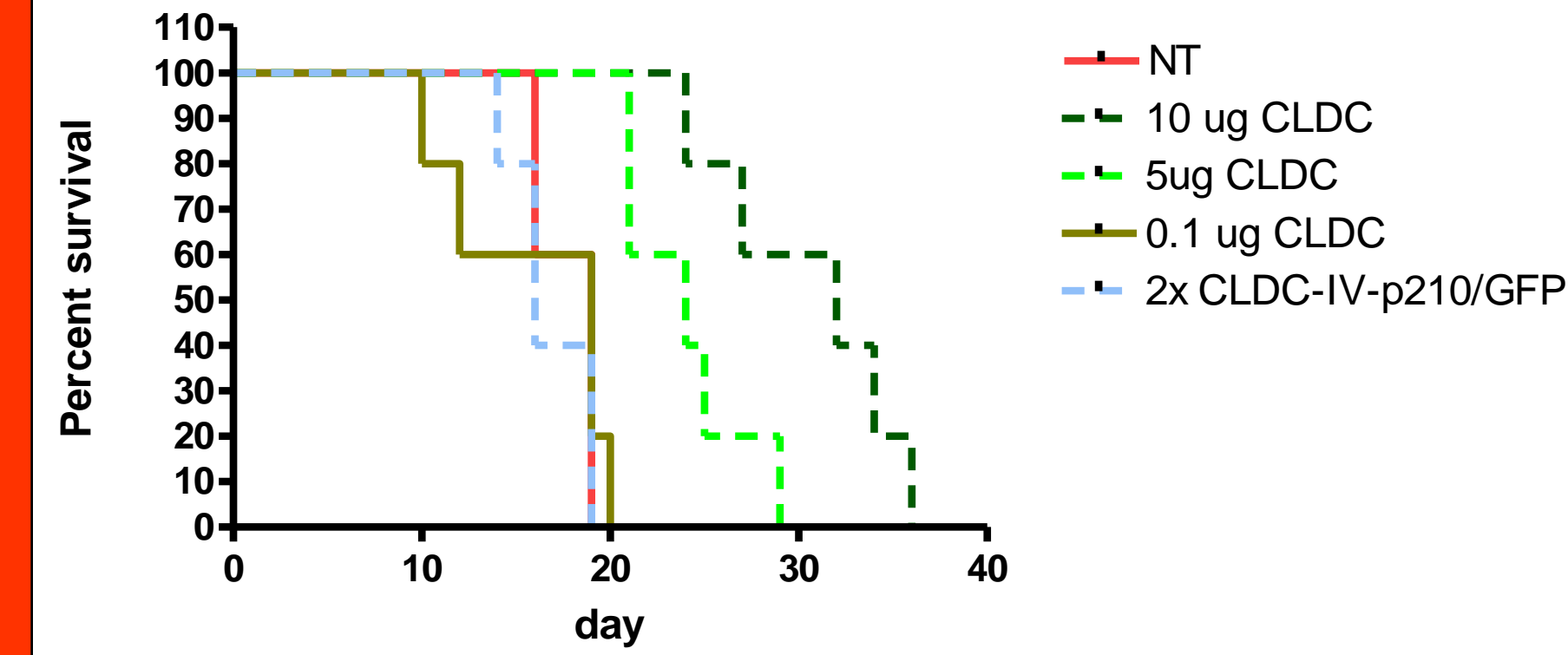
Mice were challenged with 32Dp210-GFP at day 0, Control group (red) died at day 18 to day 20 post challenge. Mice treated with 1ug JVRS-100 IV weekly after 32Dp210-GFP challenge survived until day 67

Increased Survival of Mice Treated with CLDC Following EL4 Lymphoma Challenge



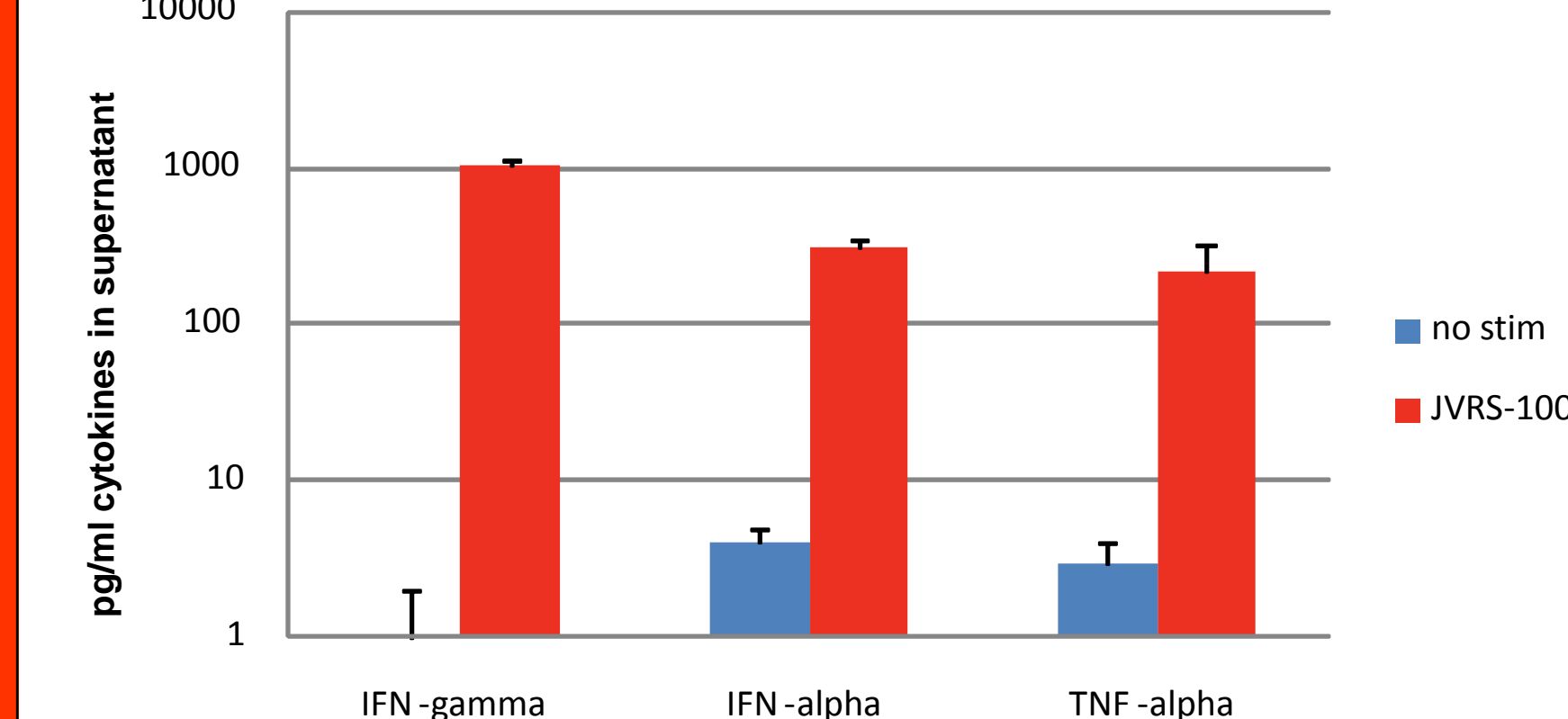
Mice were challenged with EL4 at day 0, control group (red) died at day 30 to day 36 post challenge. Mice treated with JVRS-100 IV weekly after EL4 challenge survived until day 60 (experiment ongoing).

Immunological Memory Following JVRS-100 (CLDC) Treatment



Mice were challenged with 32Dp210 on day -60; with the exception of the control group which received no challenge (blue). Mice were treated IV with JVRS-100 on Day -46 and -32; with the exception of the no treatment group (red). On Day 0 all mice were challenged with an aggressive 32Dp210-GFP to see if there was a difference in survival among untreated and treated groups in a dose dependent manner. As can be seen above, no treatment (red), 0.1ug treatment (brown), and 2x10ug JVRS-100 IV with no initial 32Dp210 challenge (blue) died at approximately Day 20. Mice challenged with 32p210 and treated with 5ug or 10ug JVRS-100 showed a 10-17 day increase in survival. This increase in survival was likely due to a specific anti-tumor response.

Cytokine Profile of Human PBMC Stimulated with JVRS-100



Human peripheral blood mononuclear cells (PBMC) were cultured *in vitro* with JVRS-100 and the culture media were analyzed by ELISA for IFN- α , IFN- γ , and TNF- α at 24 hours. PBMC supernatants were also positive for elevated levels of IL-6, IL-1 β and CCL-2 (data not shown).

CONCLUSIONS

JVRS-100 has been shown to be an immunostimulant, activating antigen presenting cells and resulting in a broad based T_H1 cytokine response. This anti-leukemic treatment effect is demonstrated here in transplantable murine models. While the treatment is highly effective and reproducible, the determination of mechanism of action, extension of these observations to other models and into the therapy of human neoplasms is clearly of interest and importance.