

Homoharringtonin overcame drug resistance and showed synergism with venetoclax in the treatment of acute myeloid leukaemia

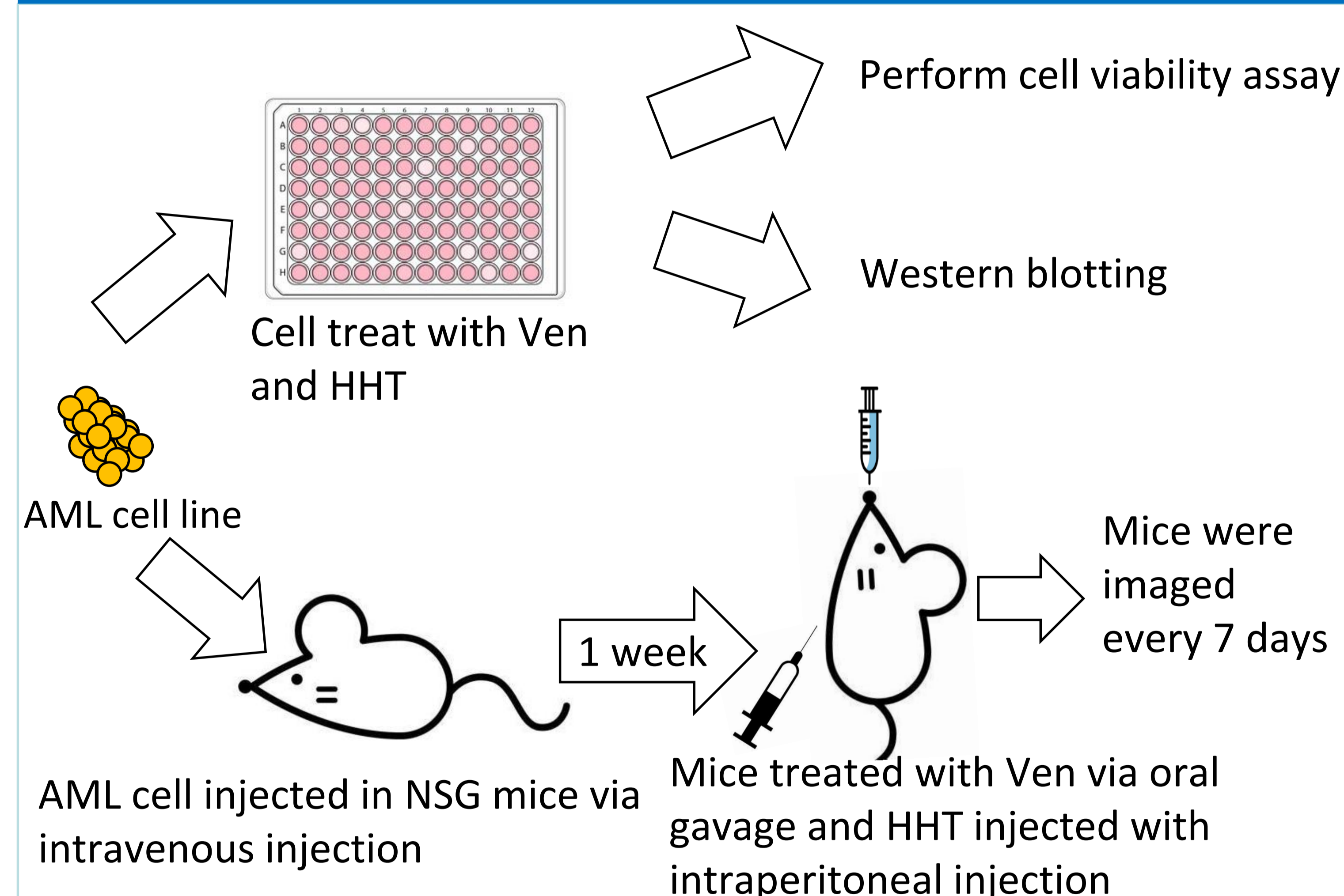
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Introduction:

- Outcome of standard treatment is dismal.
- Venetoclax (Ven), a BCL-2 inhibitor, showed effective in improving survival and remission but only 30% long term survival was observed.
- Leukaemia relapse due to emergence of Ven resistance led to treatment failure.
- We hypothesised that protein synthesis inhibitor, homoharringtonine (HHT) may overcome venetoclax resistance and combination of venetoclax and HHT will enhance the therapeutic effects of venetoclax.

Methodology:



Result:

A, Drug Response in AML Cell line

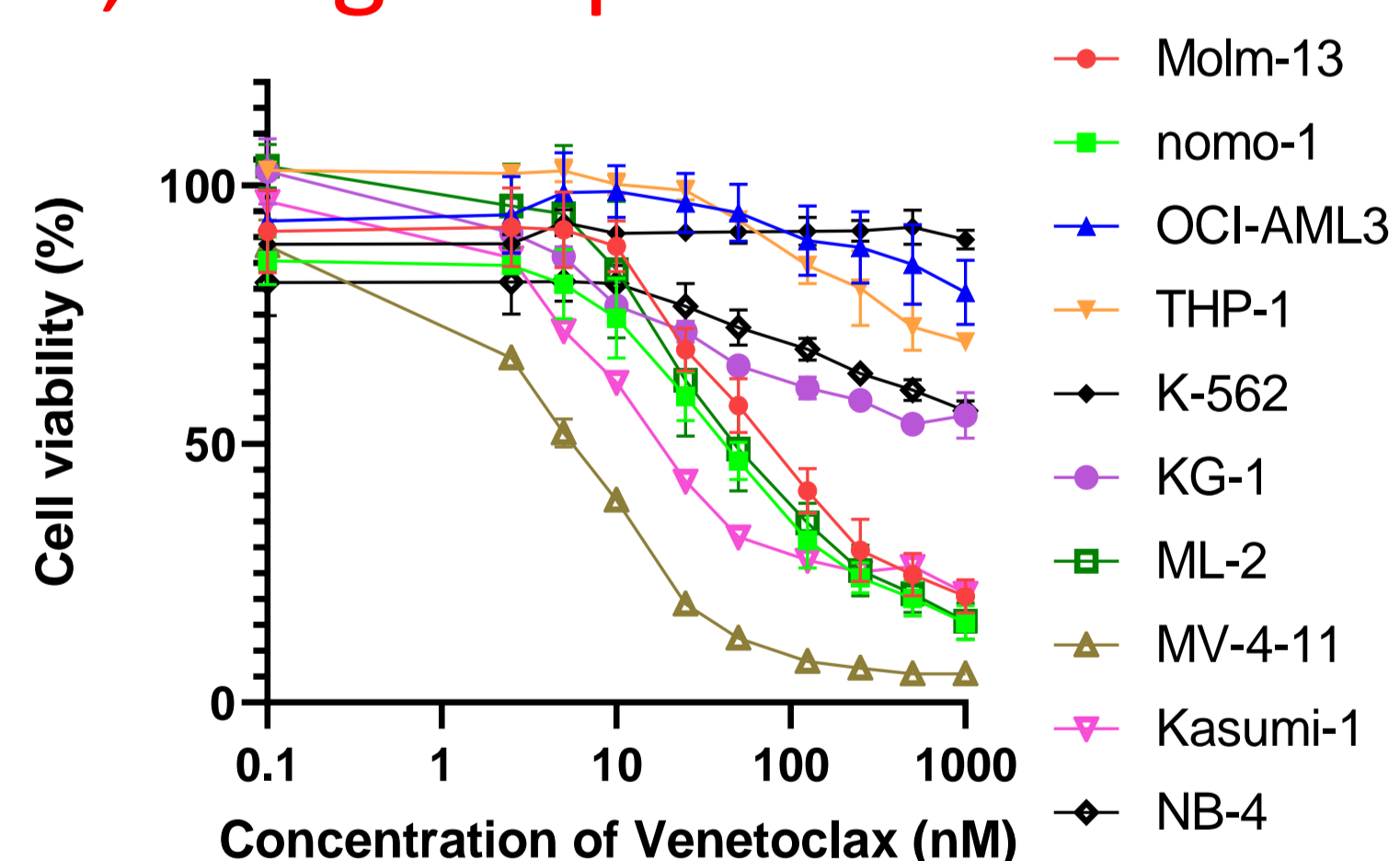


Figure 1. The Ven response in different AML cell lines. Some cell lines (OCI-AML3, THP-1, K-562 and KG-1) showed resistance to Ven.

B, Synergism of Ven and HHT

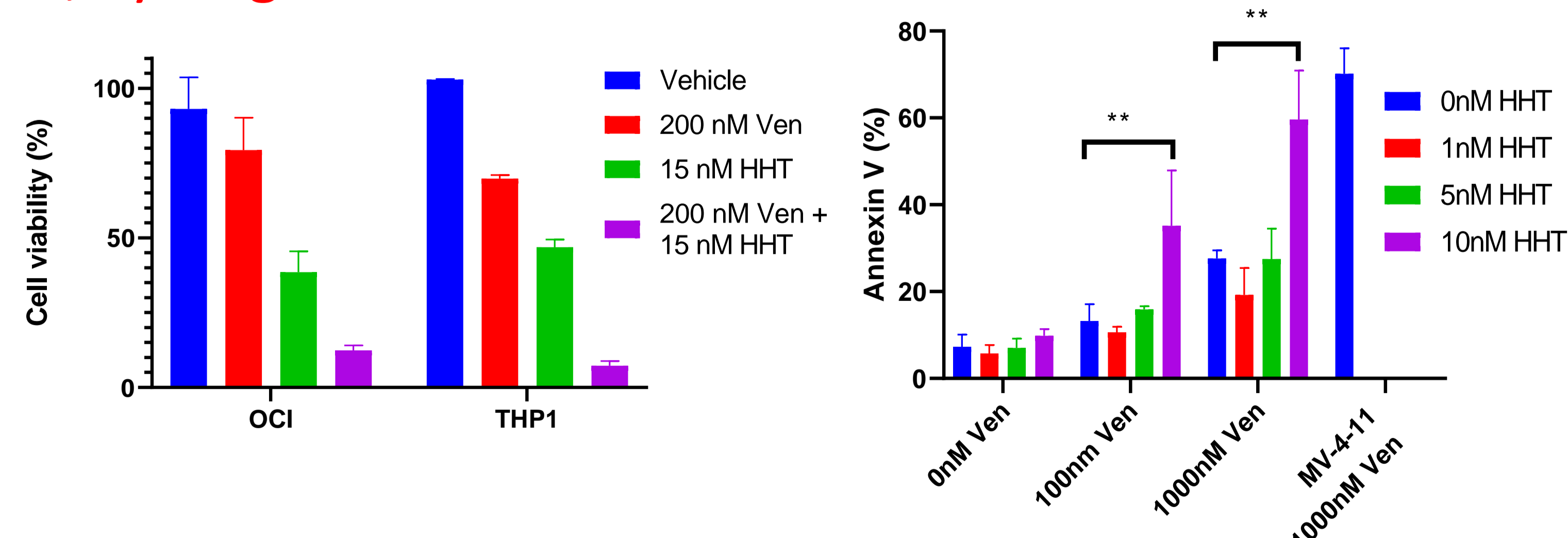


Figure 2. The response of combination of Ven and HHT was carried out in Ven resistance cell lines. Apoptosis was promoted after OCI-AML3 treated with Ven and HHT.

Result:

C, Ven with HHT also showed synergism *in vivo*

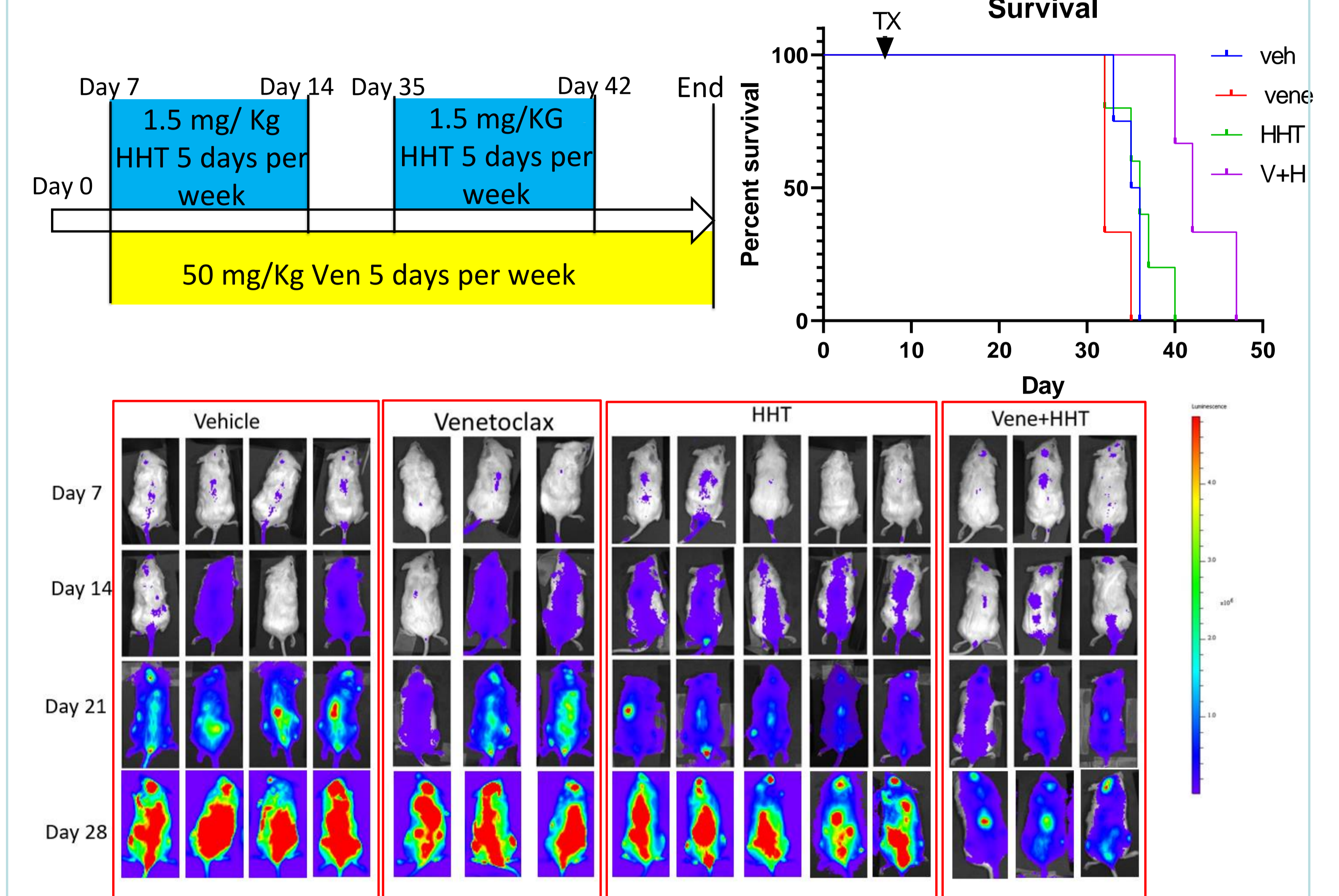


Figure 3. NOD.Cg-Prkd^{scid}//2rg^{tm1Wjl}/SzJ (NSG) mice were injected with OCI-AML3-Luc cell line. Treatment start after 1 week. 4 group of mice (A, vehicle, B, 5 days per week of 50mg/kg Ven via oral gavage, C, 5 days per months of 1.5mg/kg HHT via intraperitoneal injection, D, combine B and C) were imaged to record the engraftment.

D, Ven with HHT downregulated anti-apoptotic protein

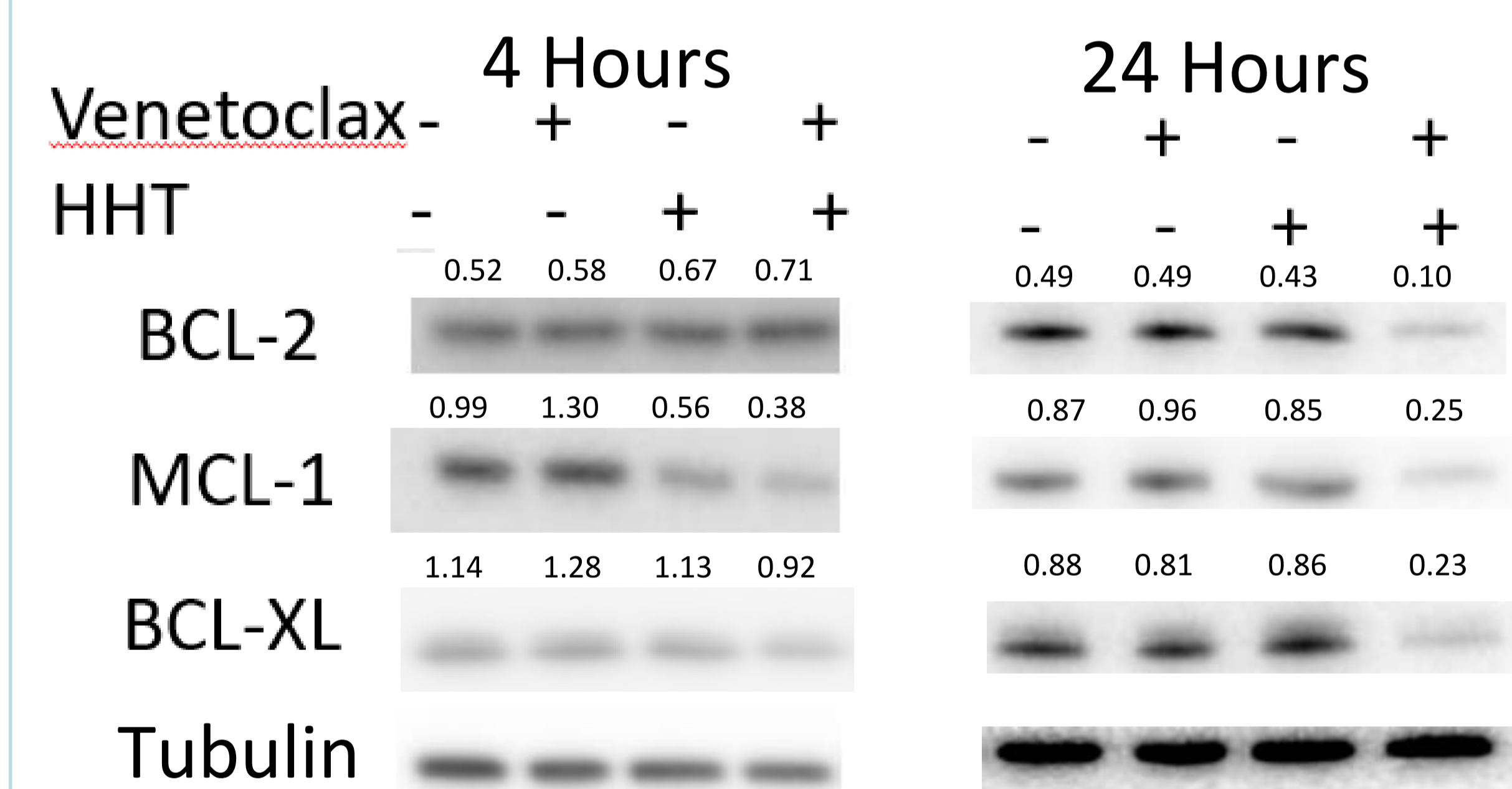


Figure 4. Western blotting of OCI-AML3 treated with 200 nM Ven and 15nM HHT for 4 hrs and 24 hrs. Anti-apoptotic protein (MCL-1 and BCL-xL) were downregulated. The intensity of bands were normalise to tubulin

Conclusion:

- HHT can overcome resistance in Ven-resistant cell line (OCI-AML3)
- HHT combine with Ven showed downregulation anti-apoptotic proteins to promote apoptosis when compare to cell treated with Ven or HHT alone.

Acknowledgement:

Croucher Foundation, Li Shu Fan Medical Foundation, Theme-based research scheme.

Reference:

Guopan Yu, Qifa Liu *et al.*; Combination of Homoharringtonine with Venetoclax and Azacitidine Excerts Better Treatment Response in Relapsed /Refractory Acute Myeloid Leukemia. Blood 2020
Courtney D. DiNardo, Anthony Letai *et al.*; Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;