PHARMACOLOGICAL INHIBITION OF TMPRSS6 DECREASES HEMOGLOBIN S CONCENTRATIONS AND RED BLOOD CELL HEMOLYSIS IN A MOUSE MODEL OF SICKLE CELL DISEASE

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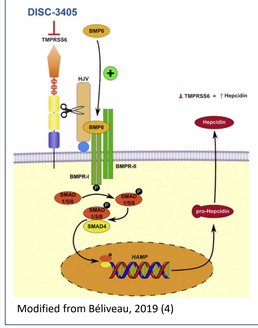
INTRODUCTION

The clinical manifestations of sickle cell disease (SCD) are due to hemoglobin S (HbS) polymerization under low oxygen conditions, which causes red blood cell (RBC) sickling and intravascular hemolysis, leading to anemia, inflammation, vaso-occlusion, and, potentially, organ failure.

Polymerization of HbS is highly dependent on HbS concentration within the RBCs (1-3). Reducing HbS concentration by iron restriction may be a viable therapeutic strategy for patients with SCD.

Hepcidin is a master regulator of iron homeostasis. DISC-3405 has the potential to increase hepcidin production, limiting iron availability and offering therapeutic benefits for SCD patients. DISC-3405 is currently being evaluated in a Phase 1 clinical study to evaluate its safety and tolerability in healthy volunteers (NCT06050915).



Modified from Béliveau, 2019 (4)

DISC-3405 is a monoclonal antibody blocking transmembrane serine protease 6 (TMPRSS6), leading to upregulation of hepcidin, reduction of iron absorption by enterocytes, and reduction of iron release from tissue stores (5-6). Iron restriction by DISC-3405 is hypothesized to reduce HbS concentration in RBCs and alleviate disease symptoms in patients with SCD.

RESULTS

Figure 1: Treatment with 10 mg/kg of r4K12B significantly increased serum hepcidin and reduced serum iron and TSAT in HbSS mice.

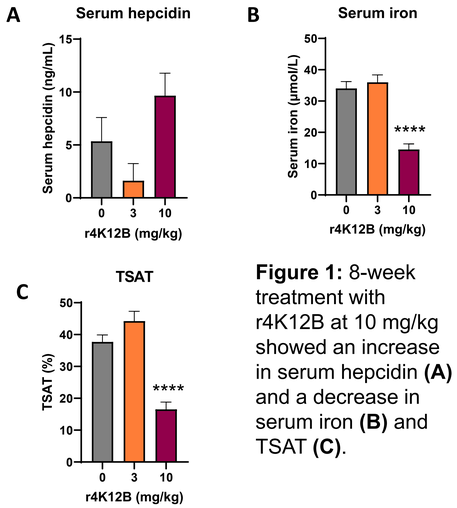


Figure 1: 8-week treatment with r4K12B at 10 mg/kg showed an increase in serum hepcidin **(A)** and a decrease in serum iron **(B)** and TSAT **(C)**.

All figures: * = p < 0.05; ** = p < 0.01; *** = p < 0.001; **** = p < 0.0001 versus 0 mg/kg group

Figure 2: Treatment with 10 mg/kg of r4K12B significantly decreased HbS concentration (CHCM) and reduced markers of hemolysis

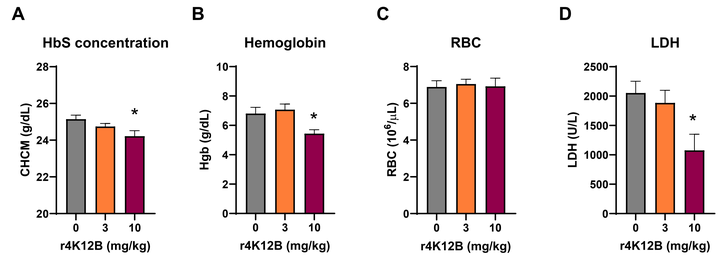


Figure 2: Iron restriction achieved by 8-week treatment with r4K12B at 10 mg/kg resulted in a significant decrease in HbS concentration **(A)** and Hgb **(B)**. No significant changes in RBC counts were observed **(C)**. LDH, a marker of RBC hemolysis, was significantly decreased after treatment with 10 mg/kg of r4K12B **(D)**. These results suggest that the iron-restricted erythropoiesis obtained with treatment with 10 mg/kg of r4K12B was balanced by decreased RBC hemolysis, resulting in unchanged RBC numbers.

CHCM = cellular hemoglobin concentration mean; Hgb = hemoglobin; LDH = lactate dehydrogenase; RBC = red blood cells

Figure 3: Treatment with 10 mg/kg of r4K12B significantly decreased spleen index and white blood cell numbers

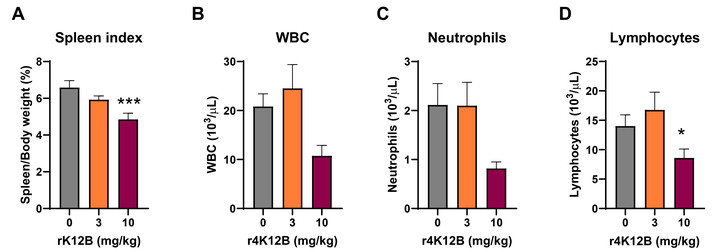


Figure 3: Iron restriction obtained by 8-week treatment with r4K12B at 10 mg/kg showed a significant reduction in spleen index compared to the vehicle-treated group **(A)** and a decrease in WBC counts **(B)**, specifically neutrophils **(C)** and lymphocytes **(D)**, suggesting decreased inflammation.

WBC = white blood cells

AIM

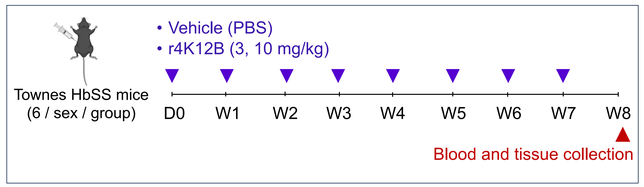
The aim of this study is to evaluate the effect of DISC-3405 in the Townes mouse model of SCD (HbSS mice).

METHODS

A murine analog of DISC-3405, r4K12B, was generated to avoid immunogenicity in mouse studies.

r4K12B was intra-peritoneally administered into 6- to 8-week-old HbSS mice once/week for 8 weeks at doses of 3 and 10 mg/kg.

Blood and tissue were collected 1 week after the last dose.



- Serum hepcidin, serum iron, and transferrin saturation (TSAT) were measured at the end of study
- Complete blood count was quantified by ADVIA hematology analyzer
- Spleen index was calculated as a percent of spleen weight over total body weight
- Data are expressed as mean ± SEM and analyzed by 1-way analysis of variance and Tukey's multiple comparison test.

CONCLUSIONS

Summary:

In the Townes mouse model of SCD, treatment with 10 mg/kg of r4K12B resulted in:

- Iron restriction with decrease in HbS concentration without affecting RBC counts.
- Decrease in LDH, suggesting decreased hemolysis
- Decrease in WBCs, suggesting reduced inflammation

Conclusion:

- Iron restriction through inhibition of TMPRSS6 may provide therapeutic benefits to SCD patients by reducing HbS concentration within RBCs.

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