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EVIDENCE OF NONINFERIORITY OF MITAPIVAT VERSUS SPLENECTOMY IN MURINE HEREDITARY SPHEROCYTOSIS

A. Matte, A. Recchiuti, E. Federti, P. A. Kosinski, V. Riccardi,
I. Iatcenko, L. Dang, A. Iolascon, R. Russo, C. Brugnara, A.
Janin, C. Leboeuf, N. Mohandas, L. De Franceschi

Disclosures

- Nothing to disclose

Hereditary Spherocytosis (HS) and Red Cell Membrane Mechanical Properties

- Hereditary Spherocytosis (HS) is the most common non-immune inherited hemolytic anemia;
- HS is due to mutation on genes encoding for red cell membrane or cytoskeleton proteins such as ankyrin, band 3, band 4.1, band 4.2 or α -, β - spectrin;
- The spectrum of clinical presentation of HS is broad, going from mild to severe anemia, requiring chronic blood transfusion regimen.

Splenectomy is a Therapeutic Option in Patients with Symptomatic HS

- Membrane mechanical instability of HS red cells accelerates erythrophagocytosis by spleen;
- In HS, the indications for splenectomy are:
 - to reduce transfusion burden (severe HS phenotype)
 - to treat symptomatic/painful splenomegaly with hypersplenism, affecting patients' quality of life (intermediate HS phenotype);
- The benefits of splenectomy in mild HS is still controversial and its cost/effectiveness might be underestimated.

Mitapivat, an Oral PK Activator, Ameliorates Anemia in Mouse Model of HS

- Relative PK deficiency has been reported in HS red cells.
- In band 4.2^{-/-} mice, a well-established model of HS, we recently show that mitapivat:
 - ameliorates anemia, reducing chronic hemolysis
 - improves RBC features

Aim of the Study

To understand whether the oral pyruvate kinase activator, mitapivat, is not less efficacious than splenectomy in treatment of anemia in 4.2^{-/-} mice.

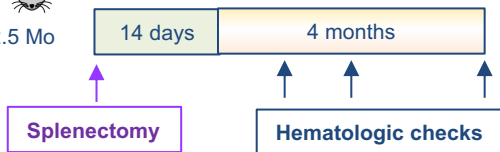
Methods

- Two to seven months-old female Band 4.2^{-/-} and C57BL6/J mice were used;
- Band 4.2^{-/-} mice were splenectomized at 2.5 months of age;
- Mitapivat (100 mg/Kg/d) was administrated for 4 months;
- CBC and reticulocytes were determined with a Sysmex Hematology Analyzer;
- Plasmatic LDH and Total bilirubin (Tbil) were determined;
- Pearls' staining was carried out on fixed livers;
- Liver iron concentration was measured using the Bathophenanthroline method.

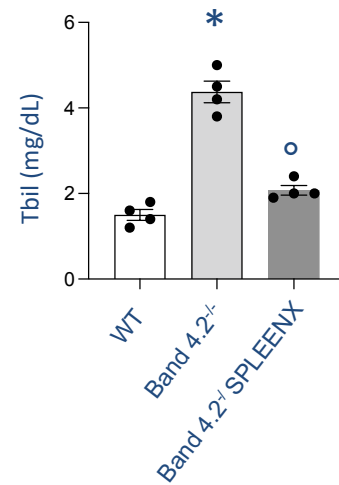
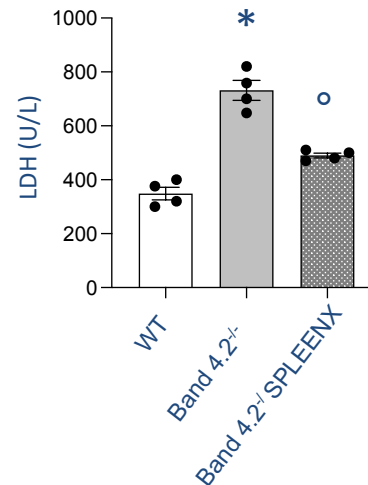
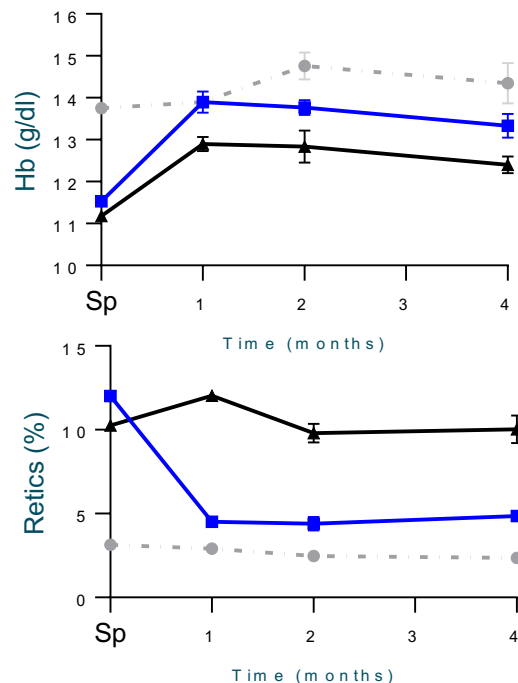
In 4.2^{-/-} Mice, Splenectomy Ameliorates Anemia and Reduces Chronic Hemolysis



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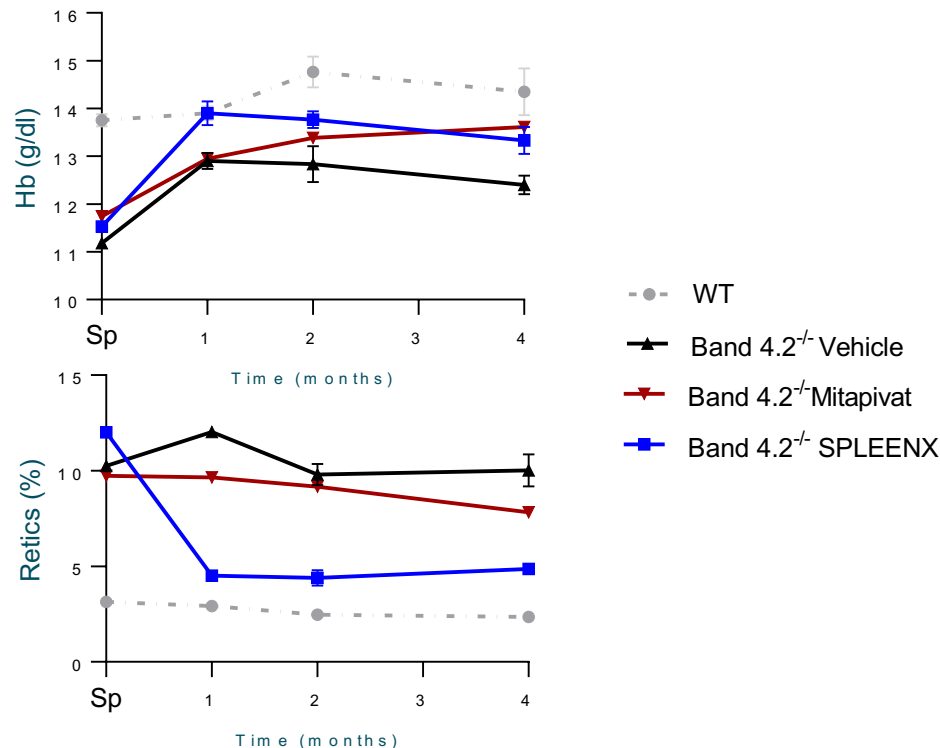
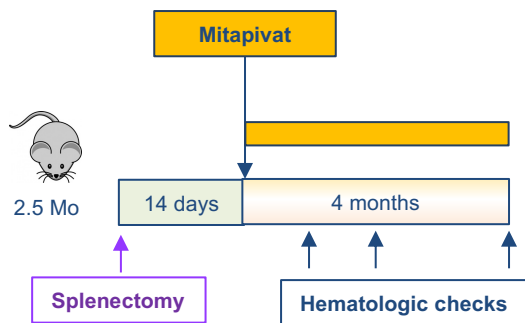


- WT
- ▲ Band 4.2^{-/-}
- Band 4.2^{-/-} SPLEENX

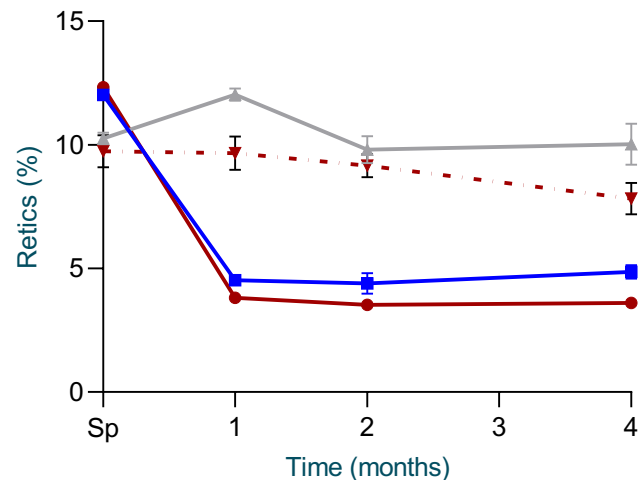
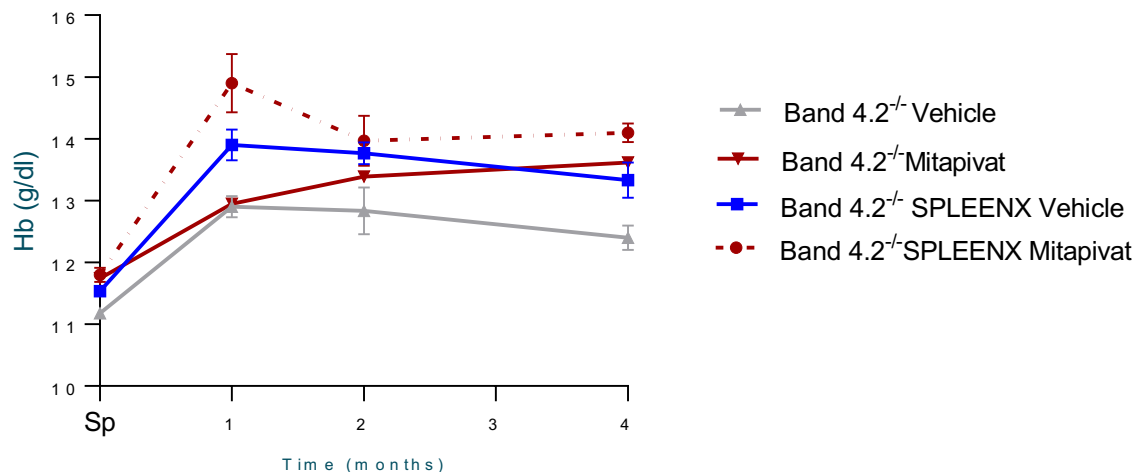


*p<0.05 compared to WT mice
 °p<0.05 compared to band 4.2^{-/-} mice

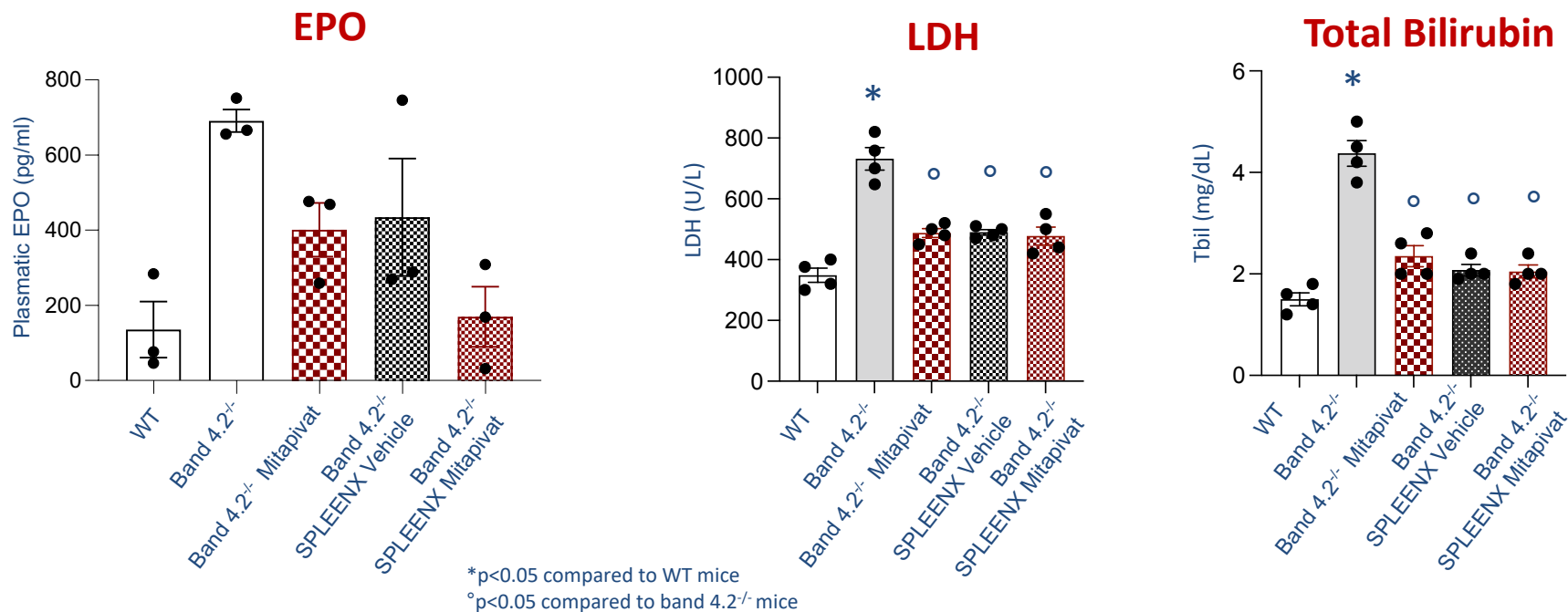
Mitapivat was not Inferior to Splenectomy for Amelioration of Anemia



Mitapivat Further Improves Anemia in Splenectomized Band 4.2^{-/-} Mice

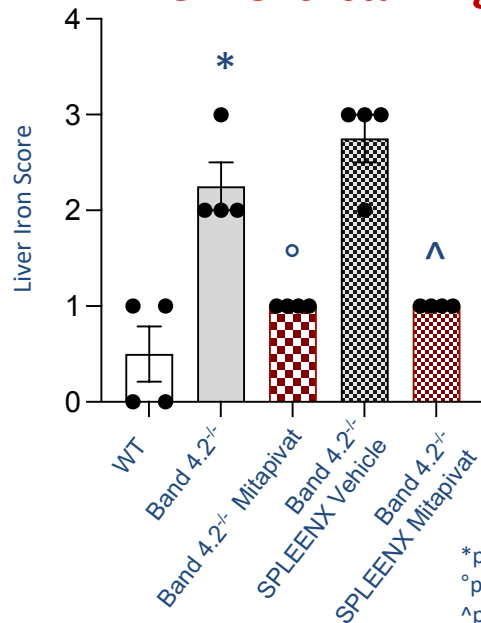


In Band 4.2^{-/-} Mice, Mitapivat was not Inferior to Splenectomy for Reduction of Chronic Hemolysis

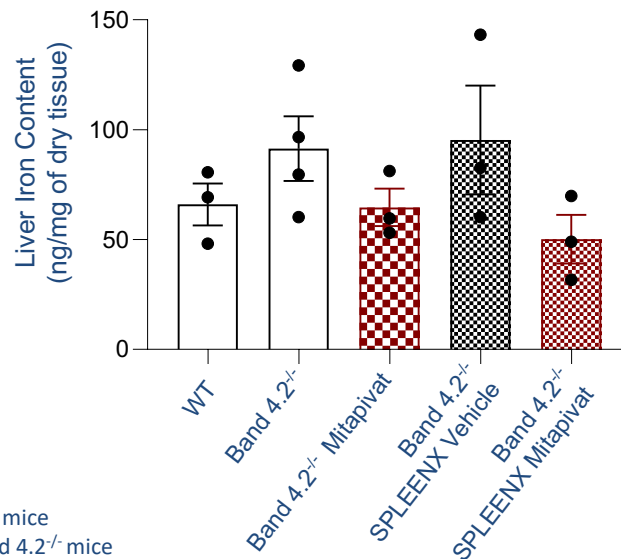


In Band 4.2^{-/-} Mice, Mitapivat was Better than Splenectomy to Reduce Liver Iron Overload

Liver Perls' staining



LIC



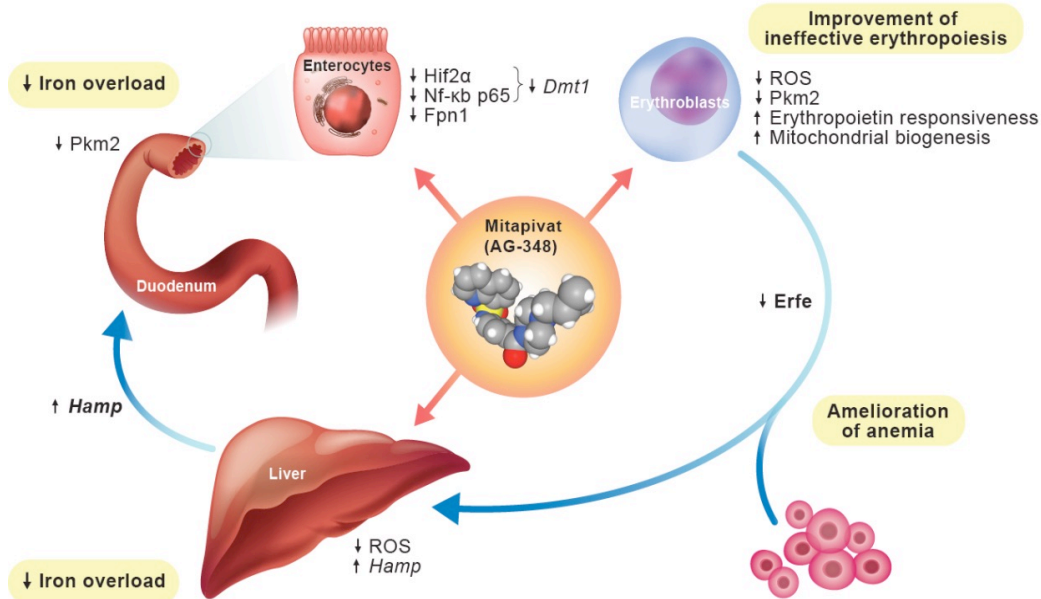
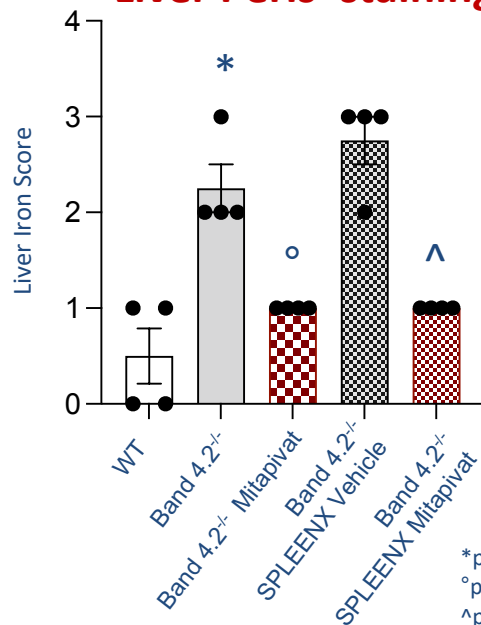
*p<0.05 compared to WT mice

°p<0.05 compared to band 4.2^{-/-} mice

^p<0.05 compared to SPLEENX Vehicle treated band 4.2^{-/-} mice

In Band 4.2^{-/-} Mice, Mitapivat was Better than Splenectomy to Reduce Liver Iron Overload

Liver Perls' staining



Conclusions

- In band 4.2^{-/-} mice, a murine model of HS,
 - Mitapivat is not inferior to splenectomy for amelioration of anemia and reduction of chronic hemolysis
 - Mitapivat is better than splenectomy in reducing liver iron overload related to chronic hemolysis.
- Our data generate the rationale to consider Mitapivat as possible therapeutic option for HS patients with intermediate hematologic phenotype in alternative to splenectomy.