Introduction

Beta thalassemia is an inherited hemoglobinopathy caused by a genetic defect in the beta-globin gene and characterised by ineffective erythropoiesis, iron overload, splenomegaly and anaemia. The role of matriline-2 (MTF-2) in iron regulation is already well established and reducing MTF-2, the gene encoding MTF-2, has shown to increase hepcidin expression and correct iron overload, splenomegaly and anaemia in Hbb\textsuperscript{αα}-/αα mice, a mouse disease model of beta thalassemia.

Here we describe a first-in-class antibody targeting MTF-2 for the treatment of iron overload diseases, such as beta thalassemia. In Hbb\textsuperscript{αα}-/αα mice, a single dose of CL-286425 decreased serum iron and transferrin saturation (TSAT) and, with repeat dosing, was able to consistently restrict iron supply thus improving hepcidin levels and splenomegaly. Furthermore, in combination with erythropoietin (epo), hepcidin levels were further improved whilst also reducing splenomegaly, usually associated with apo treatment. Together this provides evidence that treatment with an anti-MTF-2 therapy has the potential to treat iron overloaded patients, such as in beta thalassemia, to improve the anaemia and reduce iron overload resulting potentially in a lower transfusion burden and no requirement for iron chelation.

Methods

Wildtype (WT) extracellular domain (ECD) proteins of human, cynomolgus monkey, mouse and rat MTF-2 and human MTF-2 missing the serine protease (SP) domain were expressed and purified in-house. In vitro studies: human MTF-2 was used in proteolytic assay using Jing-Xia-Ang-AMC peptide substrate (Bachem). In vivo studies: 10 mg/kg of antibodies were dosed by i.p. injection into C57BL/6j mice or Hbb\textsuperscript{αα}-/αα mice bred at the Animal Research Centre (Toulouse).

Conclusions

Following screening, multiple cross-reactive (human, cyno, mouse and rat) anti-MTF-2 neutralising mAbs were successfully identified. CL-286425, shown here, inhibits MTF-2 via binding to the serine protease active site. In vivo, hepcidin levels were increased to levels comparable to that seen in Tfms\textsuperscript{αα} knockout mice (data not shown) after just 24 hours post dosing. With repeat dosing in Hbb\textsuperscript{αα}-/αα mice, there was a clear improvement in iron overload symptoms and erythropoiesis. In combination with EPO, we found that RBC number and hepcidin levels could be improved whilst the splenomegaly induced by epo stimulation could be reduced. Together, these findings suggest that beta thalassemia patients would benefit from anti-MTF-2 mAb therapy alone to improve iron overload symptoms and reduce transfusion need. Moreover, there is the possibility of an anti-MTF-2 mAb + epo combination therapy to simultaneously reduce iron overload, further improve the anaemia but not worsen the splenomegaly associated with epo alone. Further studies will explore whether the positive effect on the anaemia can be maintained whilst further reducing the splenomegaly induced by the epo co-treatment.