

Characterization of metabolic response to AG-348, an allosteric activator of red cell pyruvate kinase, in healthy volunteers and pyruvate kinase deficiency patients

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BACKGROUND

PK deficiency

- Pyruvate kinase (PK) deficiency is a glycolytic enzymopathy that causes lifelong chronic hemolytic anemia.
- PK deficiency is caused by abnormalities of the PK red blood cell isoform R (PK-R) due to mutations in the *PKLR* gene.
- Mutations in PK-R typically affect protein stability, catalytic activity, or both, which adversely affects glycolysis and leads to severe energy starvation in red blood cells.

Figure 1. Glycolytic pathway

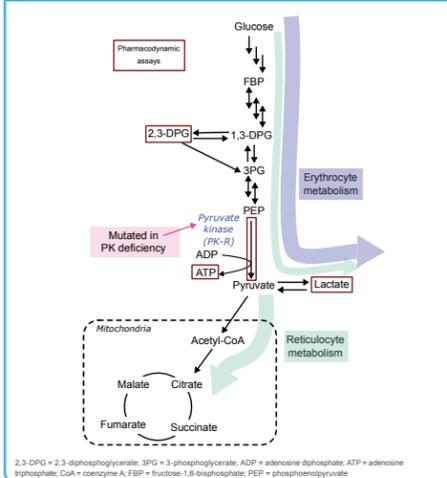
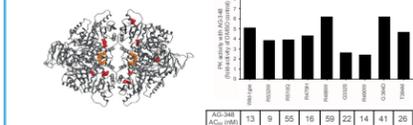


Figure 2. AG-348 is a first-in-class allosteric activator of PK-R and is in clinical development to treat PK deficiency

Phase 1 studies of AG-348 in healthy volunteers (NCT02108106, NCT02149966) have been completed, and a phase 2 study in patients with PK deficiency is ongoing (DRIVE PK: NCT02476916).



METHODS

Figure 3. Metabolic profiling and stable isotope tracing experiments were conducted in blood from healthy volunteers (n=16) and PK deficiency patients (n=8) receiving AG-348

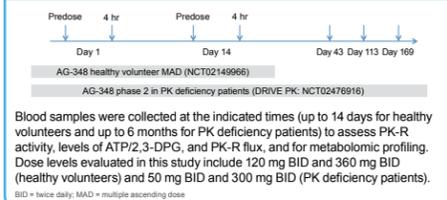
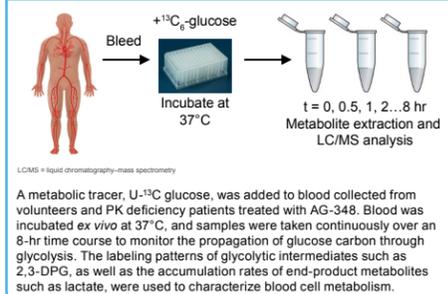


Figure 4. Ex vivo flux assay



RESULTS

Figure 5. AG-348 increases PK-R activity in healthy volunteers

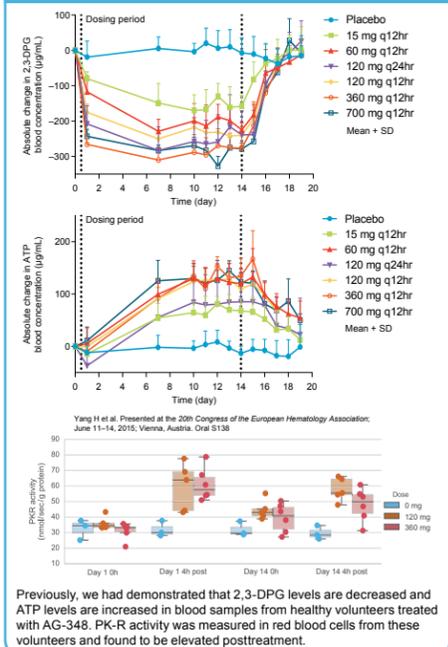


Figure 6. Healthy volunteers show metabolic markers of increased PK-R activity

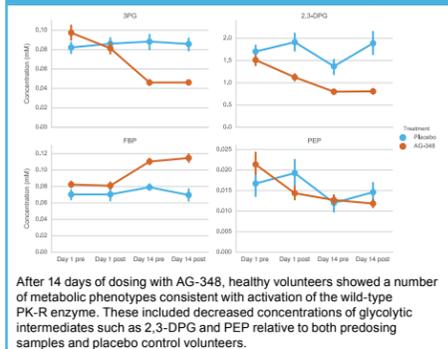


Figure 7. Overall glycolytic rates in healthy volunteers after PK-R activation remained normal

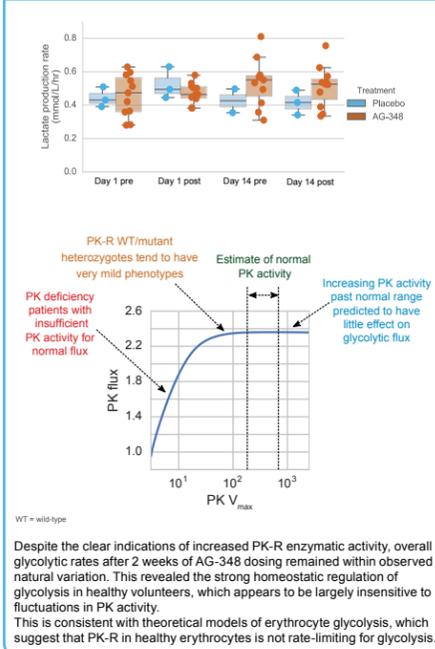


Figure 8. Metabolic analysis reveals reduced glycolytic flux in PK-deficient blood

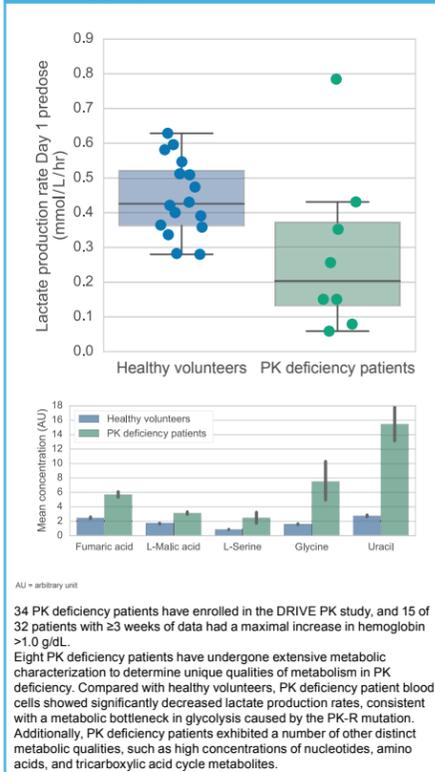


Figure 9. AG-348 rescues metabolic phenotypes in responsive patients

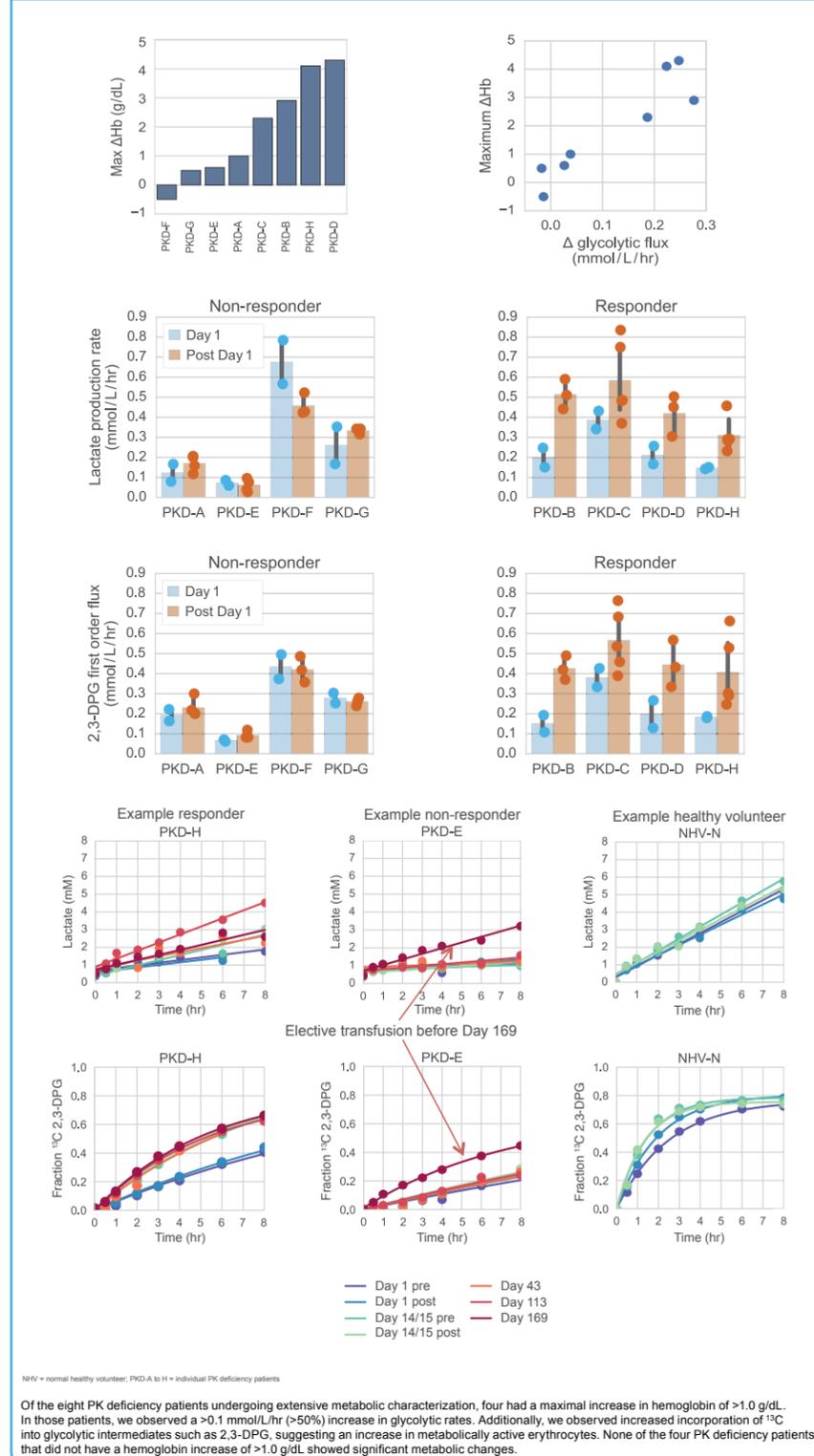


Figure 10. Independent metrics of glycolytic flux in PK deficiency patients show consistent results

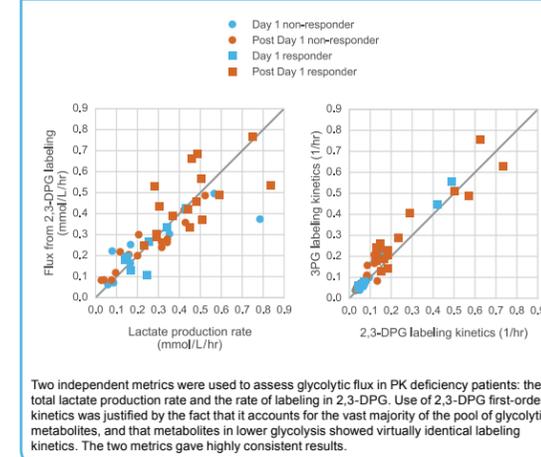
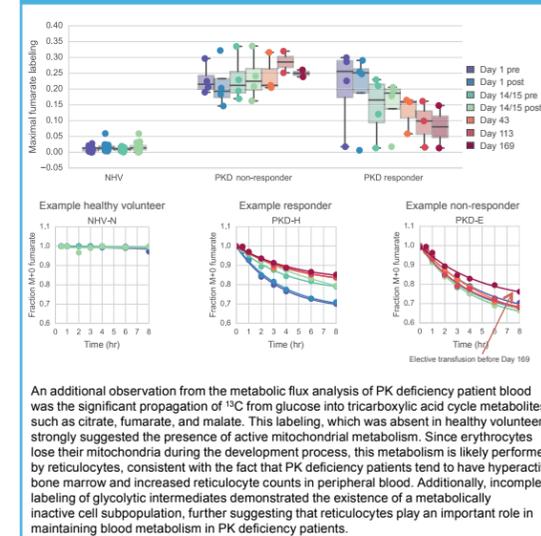


Figure 11. Metabolic markers of immature red cells are reduced in PK deficiency patients that respond to AG-348



CONCLUSIONS

- A >50% increase in glycolytic flux was observed in PK deficiency patients treated with AG-348 who had a hemoglobin increase >1.0 g/dL, but was not observed in patients without such an increase.
- Metabolic markers of immature red cells are reduced in PK deficiency patients that respond to AG-348.
- Strong homeostatic regulation of overall rates of glycolysis was observed in healthy volunteers, even in the presence of activated PK-R.
- These data demonstrate that hemoglobin increases in PK deficiency patients treated with AG-348 are associated with increased red cell glycolysis.

Disclosures
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