

**Supplementary Table S6.** *In vitro* growth selection coefficients of *pfcr*-modified and reference parasite lines.

Line	Dd2 parent	Dd2 <sup>Dd2</sup>	Dd2 <sup>Cam783</sup>	Dd2 <sup>FCB</sup>	Dd2 <sup>GB4</sup>	Dd2 <sup>3D7</sup>
s	-0.12 ± 0.007	-0.16 ± 0.007	-0.04 ± 0.011	-0.20 ± 0.009	-0.08 ± 0.014	0.00 ± 0.012
<i>P</i> <sub>1</sub>	<0.0001	<0.0001	0.03	<0.0001	<0.0001	–
Line	Dd2 <sub>R539T</sub> parent	Dd2 <sub>R539T</sub> <sup>Dd2</sup>	Dd2 <sub>R539T</sub> <sup>Cam783</sup>	Dd2 <sub>R539T</sub> <sup>FCB</sup>	Dd2 <sub>R539T</sub> <sup>GB4</sup>	Dd2 <sub>R539T</sub> <sup>3D7</sup>
s	-0.24 ± 0.007	-0.24 ± 0.006	-0.09 ± 0.010	-0.22 ± 0.006	-0.07 ± 0.01	-0.05 ± 0.01
<i>P</i> <sub>1</sub>	<0.0001	<0.0001	0.01	<0.0001	0.54	–
<i>P</i> <sub>2</sub>	<0.0001	<0.0001	0.002	0.57	0.96	<0.0001

Growth selection coefficients (s) of recombinant and parental parasite lines were determined as detailed in **Supplementary Materials and Methods**, and were normalized against the Dd2<sup>3D7</sup> line that expresses the wild-type (3D7) *pfcr* allele.  $s < 0$  and  $s > 0$  indicate growth inferior or superior to the Dd2<sup>3D7</sup> line, respectively. Listed are mean  $s \pm$  SEM values, which encompass three independent experiments performed in duplicate ( $n=6$  total replicates per line). Statistical comparisons were done using a two-way ANOVA with Sidak's post-hoc test. *P* indicates the statistical significance for *pfcr*-variant lines as compared to otherwise isogenic parasites encoding 3D7 *pfcr* (either Dd2<sup>3D7</sup> or Dd2<sub>R539T</sub><sup>3D7</sup>). *P*<sub>2</sub> indicates the statistical significance observed between *pfcr*-matched lines in the Dd2 (wild-type K13) and Dd2<sub>R539T</sub> (mutant K13) genetic backgrounds.

Color code      ns      \* $p < 0.05$       \*\* $p < 0.01$       \*\*\* $p < 0.001$