Screening of compounds from Boehringer Ingelheim's library opnMe® indicates that BI-4916, a 3-phosphoglycerate dehydrogenase inhibitor, impairs the liver stage development of P. berghei

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Plasmodium parasites that infect mammals have an obligatory development stage inside hepatocytes, which ensure proper and fast development of its exoerythrocytic forms (EEF) into infectious merozoites. Despite decades of research, a full understanding of the host molecular mechanisms required for EEF development is yet to be achieved. To identify new host pathways with importance for EEF development, we used a fluorescence-based high content imaging assay with *P. berghei* (Pb) sporozoites and HepG2 cells to screen compounds from the Boehringer Ingelheim's library opnMe®. PbEEF and HepG2 nuclei were counted; dose-response data was used to fit regressions and estimate maximum inhibition of EEF development, half maximal effect (EC50) and hepatocyte toxicity. Active compounds were further tested in different hepatocyte lines (i. e. Huh7 and HC-04) to clarify host-related effects. Among the 13 compound/control pairs tested, only BI-4916, a 3-phosphoglycerate dehydrogenase (PHGDH) inhibitor, was active against PbEEF [EC50=1,22 ± 1,20 μM (Geo. Mean ± SD)] with incomplete inhibition of HepG2 proliferation [Selectivity Index (SI)=29,64] and negligible effect of the corresponding scaffold control. PHGDH is a rate limiting enzyme that catalyzes the *de novo* synthesis of serine and is hypothesized to be absent in malaria parasites. To investigate if the effect was host-related, the assay was performed in Huh7 and HC-04 as well. Results obtained were similar between HC-04 and HepG2; however, Huh7 showed increased susceptibility to BI-4916, leading to overlapping effects between Huh7 and PbEEF dose-response curves (SI=1,26). In theory, *Plasmodium* blood stages rely on serine scavenging through hemoglobin digestion; as this is missing during EEF development, *Plasmodium* might have evolved to find additional serine sources in the metabolic active hepatocyte. We might have identified that source and that host's PHGDH is required for the EEF development of malaria parasites.