To assess whether direct MET activation causes substantial differences in parasite invasion or development rates, we infected HepG2-CD81 cells with *P. yoelii* or *P. berghei* after treatment with either HGF or the MET inhibitor SU11274. We found that HGF pretreatment led to an increase in *P. berghei* EEFs, whereas MET inhibition led to fewer *P. berghei* EEFs (**Fig. 1c** and **Supplementary Fig. 2**), in agreement with Carrolo *et al.*[3]. However, no difference in *P. yoelii* EEF burden was seen after modulation of MET signaling (**Fig. 1c** and **Supplementary Fig. 2**).

Taken together, our data suggest that, unlike *P. berghei*, neither *P. yoelii* nor *P. falciparum* activates MET signaling upon cell traversal. Furthermore, *P. yoelii* host cell invasion and EEF development do not seem to be affected by MET activation or inactivation. All three species traverse HepG2-CD81 cells at comparable rates, suggesting a particular trait unique to *P. berghei* cell traversal that leads to HGF secretion. Furthermore, *P. berghei* invasion, early development or both have a stronger dependency on MET. This is particularly interesting in light of the observations that *P. berghei* is less selective in its host cell than other *Plasmodium* species. For instance, *P. berghei* can readily infect HepG2, Hepa1-6 and Huh7 and nonhepatocytic cells, whereas *P. yoelii* and *P. falciparum* require CD81 to invade cells[7] and only develop in hepatocyte-derived cells. Recently, it has been demonstrated that *P. berghei* EEFs develop fully inside the skin of the mouse[8], but similar evidence for other rodent *Plasmodium* species is less direct[9], and none exists for *P. falciparum*. One possibility is that *P. berghei* is able to use receptor tyrosine kinase signaling, which is available in nearly all cell types and lines, to facilitate invasion and early development, whereas other *Plasmodium* species such as *P. yoelii* and *P. falciparum* require more specialized molecules including but not limited to CD81, combinations of which are only provided in a very small number of hepatocyte-derived cell lines or on primary hepatocytes.

Our findings are consistent with the few instances of published data comparing the impact of host signaling in the two rodent parasite species. Cunha-Rodrigues *et al.*[7] recently showed that genistein, a dietary supplement that acts at least in part by inhibiting MET activation, lowers *P. berghei* liver stage burden in mice. However, higher levels of genistein are required to reduce *P. yoelii* EEFs *in vitro*. Identifying previously unknown signaling proteins in the hepatocyte that are required for invasion and liver stage development remains a crucial point of investigation, but caution should be taken to ensure that findings are broadly applicable to malaria parasites in general, including those infecting humans.

COMPETING FINANCIAL INTERESTS
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Alexis Kaushansky[1] & Stefan H I Kappe[1,2]

[1]Seattle Biomedical Research Institute, Seattle, Washington, USA. [2]Department of Global Health, University of Washington, Seattle, Washington, USA.
e-mail: stefan.kappe@seattlebiomed.org

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Rodriguez and Mota reply:

We previously showed that migration of *Plasmodium berghei* sporozoites through hepatocytes causes cell wounding and leads to the release of hepatocyte growth factor (HGF) and the activation of its tyrosine kinase receptor, MET. We also showed that MET activation boosts *P. berghei* infection in mice, whereas its depletion leads to a reduction in infection[1,2]. Now, Kaushansky and Kappe, although fully confirming our data with *P. berghei*, further show that neither *Plasmodium yoelii* nor *Plasmodium falciparum* sporozoite migration through hepatocytes activates MET. The authors use this system to highlight the similarities between *P. falciparum* and *P. yoelii* versus *P. berghei*. As the authors clearly state, *P. berghei* is less selective for its host cell than other *Plasmodium* species, as it is able to infect several hepatoma cell lines as well as several nonhepatocytic cells in a CD81-dependent or CD81-independent manner *in vitro*[3]. In contrast, *P. yoelii* and *P. falciparum* require CD81 to invade cells and are much more restricted in the range of cells they can infect *in vitro*. Nevertheless, *P. falciparum* and *P. yoelii* also differ quite markedly from each other. Although neither of them can infect HepG2 cells, expression of CD81 makes these cells susceptible to *P. yoelii* but not to *P. falciparum* infection. In contrast, certain aspects of the *P. berghei* model of liver stage infection resemble another important human pathogen, *Plasmodium vivax*. Indeed, like *P. berghei*, *P. vivax* readily infects HepG2 cells, indicating that both parasites are able to infect cells in a CD81-independent manner[4]. Altogether, although these studies emphasize the limitations of the currently available *Plasmodium* rodent models, these models are nevertheless very useful and often constitute the only possible approach to reveal and dissect the mechanisms underlying *Plasmodium* infection. Furthermore, all of these studies also highlight how the different *Plasmodium* species have evolved different mechanisms to infect their hosts. Understanding how these mechanisms were acquired and their role in virulence and infection will certainly contribute to improved design of future strategies to combat malaria.

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Ana Rodriguez[1] & Maria M Mota[2]

[1]Department of Microbiology, Division of Medical Parasitology, New York University School of Medicine, New York, New York, USA. [2]Unidade de Malária, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal.
e-mail: mmota@fm.ul.pt

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