# Review of: "Rough and smooth variants of Mycobacterium abscessus are differentially controlled by host immunity during chronic infection of adult zebrafish"

Jean-Louis Herrmann[1], Hamadoun Touré, Marion Lagune

1 Assistance Publique – Hôpitaux de Paris

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In this well-written and clear paper, Kam and collaborators propose a chronic infection model in adult Zebrafish for studying both S and R *M. abscessus* variants pathophysiology. This model can be used to decipher the pathophysiology and potential therapeutic-screening of chronic *M. abscessus* infection, which was not possible with most existing models. Authors highlighted requirement of different arms of the immune system (*i.e.* TNF and T cells) for controlling respective infections with both morphotypes. However, we have some reservations regarding the real impact of these different arms on the worsening or alleviation of the infection by both morphotypes, due to the lack of survival curves corroborating the pathophysiological observations in the Figures 2 to 4 and 6.

We list the specific strengths, limitations, and our comments to parts of the article as follows:

- Authors observed more significative formation of necrotic granulomas in the R variant-infected fishes compared to the S ones on days 10 and 14 post-infection. This observation is consistent with the formation of granulomas by both morphotypes observed in the zebrafish embryo (Bernut *et al.*, 2014) and demonstrates the similarity of some features of the infection between the two-host development.
- Furthermore, this model seems to be adequate to study the pathogenesis of the different morphotypes of *M. abscessus* as it corroborates results obtained in the cell model (Roux *et al.*, 2016)
- Using dexamethasone and TNF deficient fishes (*tnfa*, *tnfr1* and *tnfr2*), authors observed a protective role of TNF-mediated immunity against the S morphotype infection and a detrimental one against the R morphotype through granuloma necrosis. This observation is specific to the adult zebrafish. Indeed, as mentioned by the authors, TNF is critical for zebrafish embryos survival during infection with both morphotypes (Bernut *et al.*, 2016). Some experiments conducted in mice point in the same direction (Rottman *et al.*, 2007. This is also supported by the fact that defective patients for TNF are more prone to *M. abscessus* infection (Chan *et al.*, 2016). The authors should have discussed this part of the paper in more depth and proposed strong hypotheses, especially since this part is one of the main messages of the paper. The authors' assumption that the susceptibility of patients defective for TNF is a shortcut.
- Authors show T cells involvement for containing the R morphotype granulomas. It would have been nice if the authors would have discussed and hypothesized about the links and kinetics of granuloma necrosis through the TNF pathway and T cell involvement. Also, it would have been interesting to know which of these two responses is predominant over the other with epistatic experiments for example.
- Authors hypothesize that the absence of *M. abscessus* infection in AIDS patients in comparison to other NTM or *M.*

*tuberculosis* is due to the limited impact of T cell to control*M. abscesus* S morphotype. However, these results should be contrasted with those obtained in other models. Indeed, in mice infected by *M. abscessus* S morphotype, the T cell response was shown to limits *M. abscesus* burdens (Rottman *et al*., 2007).

Globally, Kam and collaborators produce a well-designed experimental study and provide an interested animal model to decipher *M. abscessus* pathophysiology in the context of innate and adaptive immune response, until now only a mice model was commonly used with both immunities. Nevertheless, it would have been appreciated if in the discussion, the results obtained in this model could have been put in regards with those already obtained in other models.