Translational challenges in visceral leishmaniasis drug development: different models, different drugs' mechanism of action, different predictive value: towards an emerging answer?

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BACKGROUND

New safe, low cost, and field-adapted drugs for visceral leishmaniasis (VL) are urgently needed. Despite substantial screening and lead optimization efforts during the last ﬁve years within various organizations, few new chemical entities have successfully entered into the clinic. Whether the right tools or the correct decision-making processes are being used to progress compounds should therefore be reviewed. E.g. VL animal models need to be standardized, and variability linked to the animal or Leishmania species used, as well as readouts, should be assessed in a careful and systematic way.

THE CHALLENGE

Leishmania: complexity & challenges

HOW CAN WE DESIGN & SELECT NEW VL DRUG CANDIDATES?

- General lack of systematic data generated
- Lack of targets/target validation and translation into whole cell activity
- Determination of activity/rate of kill in vivo is not well described
- Lack of cross-validation and standardized in vitro and in vivo models (species, treatment regimen, duration, readouts, ...)
- NIVC difficult
- Lack of translational understanding/human prediction, clinically validated targets
- MOA/PK/ID of current triazoles is not well understood
- Chemical structures or PK profile of current treatment are unusual
- Regional treatment sensitivity differences (East Africa vs India): Host genetic background, Leishmania strains

CONCLUSIONS AND PERSPECTIVES

Even if mouse and hamster models are diﬀerent in several aspects, the ﬁrst being notably more appropriate during Lead Optimization and the second being closer to human clinicopathology, this analysis shows that they both lead to the same outcome, irrespective of the class of compounds. However, and when applicable, it remains appropriate to test any promising compounds in both models, as this would provide some reassurance that the results are relevant for humans, not just mice or hamsters. Considering the particular case of tafenoquine which accumulates in the liver, or miltefosine that needs at least 5 days to reach a steady state and still cirulates at high concentration 2 days after end of dosing, several questions remain to be answered, and tools need to be developed in order to avoid mistakes in late compound progression: What about the parasite burden/tropism in diﬀerent models as it relates to the tropism of the compounds themselves? Can we solve this issue with biomimescence models? Is it essential to measure the volume of distribution? Do we need to target 100% activity in in vitro assays and sterile cure in in vivo models? Is an IV, IP or co-ABT dosing acceptable for a Proof-of-Concept? Can we better understand what is needed by doing animal POP-PK analysis? And finally, do these animal models translate to the situation in man?

Hopefully, these questions will be answered in the near future when clinical trial data starts to be generated for the promising NCIs currently in preclinical development.