## *Leishmania* as a paradigm for exploring the impact of genome diversity on metabolome variation

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The genome and the metabolome are situated at the extreme ends of the modern dogma of molecular biology, representing the genetic potential and its metabolic realisation. The natural diversity of microorganisms provides the context for innovative studies on the functional link between these two '-omes'. We use a Nepalese population of *Leishmania donovani* (Protozoa, trypanosomatids) which combines a very recent clonal origin (low sequence heterogeneity) and a high phenotypic diversity (antimonial drug susceptibility, infectivity, …). This population is now being characterised with the next generation sequencing technologies for genomics studies and state-of-the-art LC-MS for whole-metabolome characterisation.

Full-genome sequencing of 17 *L. donovani* lines revealed a low diversity at the sequence level, but a high diversity at the structural level (aneuploidy, tandemly repeated genes, episomes) [1]. We hypothesise that this structural variation drives the evolutionary flexibility and adaptive capacity of *L. donovani*. We are currently investigating how the observed diversity on genome level is manifested on the level of metabolic diversity. A proof-of-principle metabolomics study which characterised two clinical lines with LC-MS highlighted the potential of untargeted metabolic profiling to reveal global metabolic differences between antimonial-sensitive and antimonial-resistant *L. donovani* lines. One third of all detected metabolites proved to have significant different levels in the two phenotypes [2]. A similar global metabolomics characterisation is currently in progress for all clinical lines which were studied on genome level. The resulting metabolome diversity data will be related to the genomic diversity data for all 17 clinical lines. We anticipate that this integrative approach will give an unprecedented insight into pathogen diversity.

References

[1] Downing T., et al. **2011**. Whole-genome sequencing of *Leishmania donovani* clinical lines reveals dynamic variation related to drug resistance. Submitted.
[2] t'Kindt R., et al. **2010**. Metabolomics to unveil and understand phenotypic diversity among pathogen populations. *PLoS Negl Trop D.*411, e904.