Human African trypanosomiasis biomarkers: from discovery to translation towards field applications

Natalia Tiberti1, Veerle Lejon2, Alexandre Hainard1, Bertrand Courtioux3, Enoch Matovu4, John Charles Enyan5, Xavier Robin1, Natacha Turck1, Krister Kristensson6, Dieudonné Mumba Ngoyi7, Sanjeev Krishna8, Sylvie Bisser3, Joseph Mathu Ndung'u9, Philippe Büscher10, Jean-Charles Sanchez1

1 Biomedical Proteomics Research Group, Medical University Centre, Geneva, Switzerland; 2 Institut de Recherche pour le Développement UMR 177 - Intertryp Campus International de Baillarguet, Montpellier, France; 3 INSERM UMR1094 Tropical Neuroepidemiology & Institute of Neuroepidemiology and Tropical Neurology, University of Limoges, France; 4Department of Biotechnical and Diagnostics Sciences, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda; 5Department of Biochemistry, College of Natural Sciences, Makerere University, Kampala, Uganda; 6 Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden; 7 Department of Parasitology, Institut National de Recherche Biomédicale, Kinshasa, D.R. Congo; 8 Centre for Infection, Division of Cellular and Molecular Medicine, St. George's, University of London, Great Britain; 9 Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland 10 Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.

Introduction Human African trypanosomiasis (HAT) is a neglected parasitic disease affecting rural communities in sub-Saharan Africa. The disease progresses from a first haemolymphatic stage (S1) to a second meningo-encephalitic stage (S2), when trypanosome parasites penetrate into the central nervous system. Determination of the stage of disease and early detection of relapses during the post-therapeutic follow-up represent key issues to properly and safely treat patients. Current methods, based on counting of the white blood cells (WBC) and the detection of parasites in the cerebrospinal fluid (CSF) are, in fact, either not specific or not sensitive enough.

Methods and key results In this project we investigated CSF from HAT patients using different approaches, including proteomics and hypothesis driven discovery to highlight new promising markers. Eight candidates were identified to be able to stratify patients according to the stage of disease progression. Following their evaluation on a multicentre cohort, neopterin was validated as a powerful CSF staging marker for T. b. gambiense HAT. This metabolite, at a concentration of 14 nmol/L, was able to accurately discriminate between S1 and S2 patients before treatment (SP 88%, SE 88%). Interestingly, neopterin resulted also to be the best test-of-cure marker being able to discriminate between cured and relapsed S2 patients as soon as 6 months after treatment with 87% specificity and 92% sensitivity and showing higher accuracy than WBC.

Conclusions In order to translate this marker into a field test, a first prototype of point-of-care testing (POCT) has been produced. Its first evaluation on stored samples has shown the feasibility of the assay for rapid neopterin detection in the CSF and promising results for both staging and test of cure applications. Further optimization will be crucial to translate this POCT into the field to ameliorate patients’ management and to contribute to HAT control.