Drug resistance prior to exposure!

Animal trypanosomes and the diminazene aceturate (DA)-resistance linked mutation.

Review by: Emily Dawson, PhD student, University of Nottingham.

Buffalo from Kruger Park, South Africa. *T. congolense* is a major livestock pathogen in Africa. (Image kindly provided by Vincent Delespaux, Institute of Tropical Medicine, Antwerp, Belgium.)

A recent paper published in PLoS NTDs by Chitanga *et al.* (2011) has demonstrated that the presence of a mutation associated with resistance to DA is present in *T. congolense* isolates from wildlife without a history of drug exposure. *Trypanosoma congolense* transmitted by the tsetse fly causes animal trypanosomiasis, a disease which contributes to the loss of millions of livestock in Africa each year. Control of the parasite relies largely on the use of trypanocidal drugs, such as diminazene aceturate (DA).

Chitanga *et al.* used *Dpn*II-PCR-RFLP to screen for the DA-resistance linked mutation in 34 *T. congolense* isolates taken from infected tsetse flies or infected buffaloes. The mutation was present on at least one allele of 33 of these samples.12 of the isolates were successfully grown in mice, and these mice treated with DA at either 10mg/kg or 20mg/kg. 51.4% of the mice treated at 10mg/kg remained positive for trypanosomes after 8 weeks, with 38.9% remaining positive after treatment with 20mg/kg (determined using 18S-PCR). Microscopy indicated a much lower rate of trypanosome positivity at 8.3% and 0% respectively.

A high prevalence of the DA-resistance linked mutation (97.1%) in regions where the trypanosomes have never been exposed to any trypanocidal drug pressure is surprising. Mutations conferring drug resistance are usually related to a fitness cost for the parasite and can often be selected out when the drug pressure is removed. The results presented by Chitanga *et al.* suggest the contrary: complete elimination of the use of DA would not allow for a return to drug sensitivity. The mutation may be a part of the normal genotypic diversity of wild trypanosome populations and confer a selective advantage over non-mutated strains.

Although one may be inclined to think that these results call for an end to the use of DA, the fact that few mice were microscopically-positive following treatment at 10mg/kg, and none at 20mg/kg, may suggest that its use will allow the host to control *T. congolense* and the corresponding disease to an acceptable level.

Full reference: **High Prevalence of Drug Resistance in Animal Trypanosomes without a History of Drug Exposure.** 2011. Simbarashe Chitanga et al. *PLoS NTDs*, **5**, e1454. http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0001454#aff1

Emily Dawson is a second year PhD student at University of Nottingham under the supervision of Professor Mike Doenhoff. She is working on the development of a rapid diagnostic test (RDT) for schistosomiasis from whole blood.