Diversity of aquaglyceroporin genes (*TbAQP)* in *Trypanozoon* and their relation to melarsoprol and pentamidine cross-resistance (MPXR)

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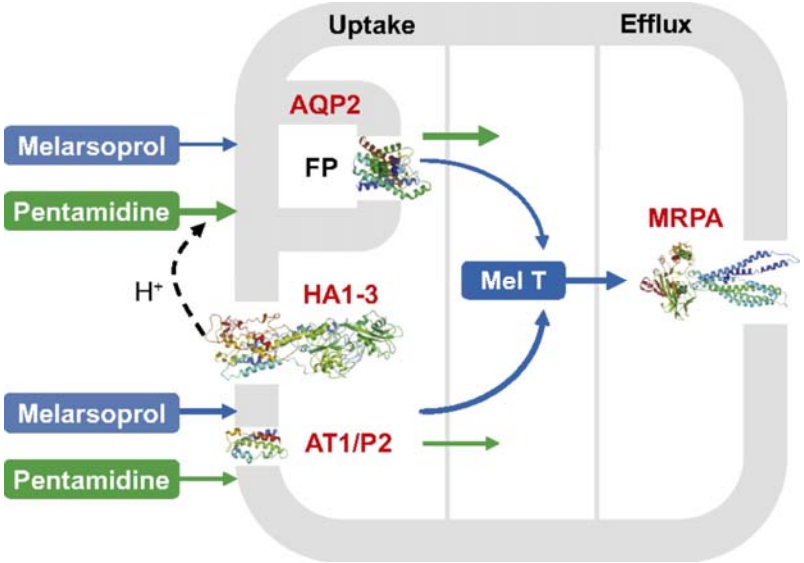
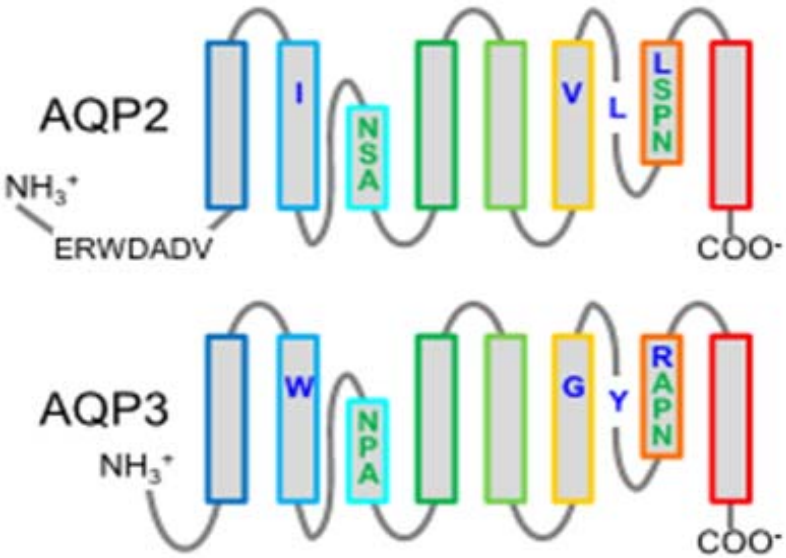
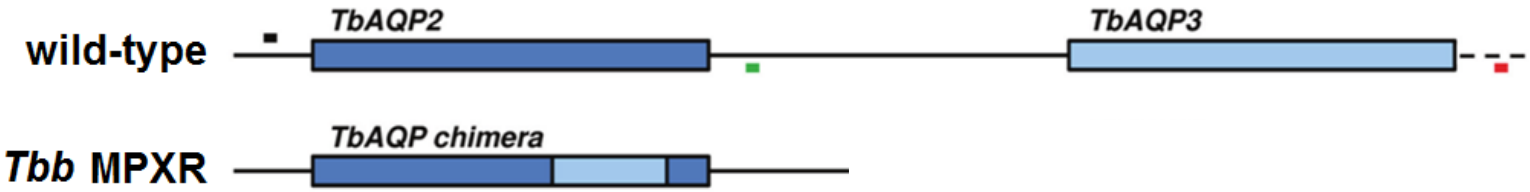
MPXR in HAT



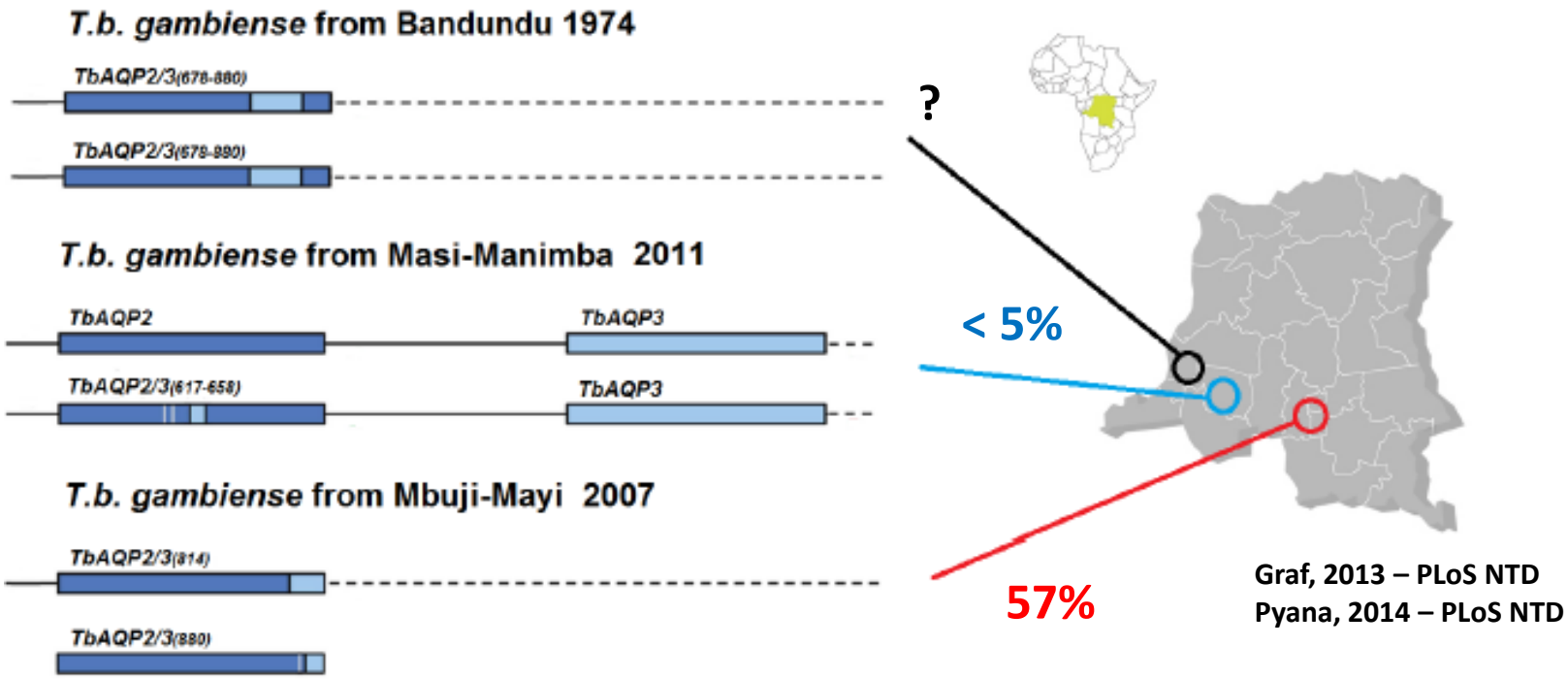
Baker, 2012 - PNAS



Baker, 2012 - PNAS

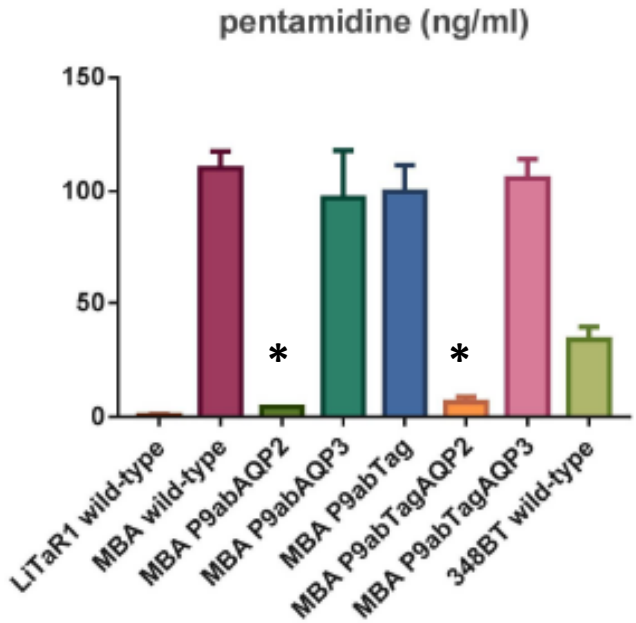


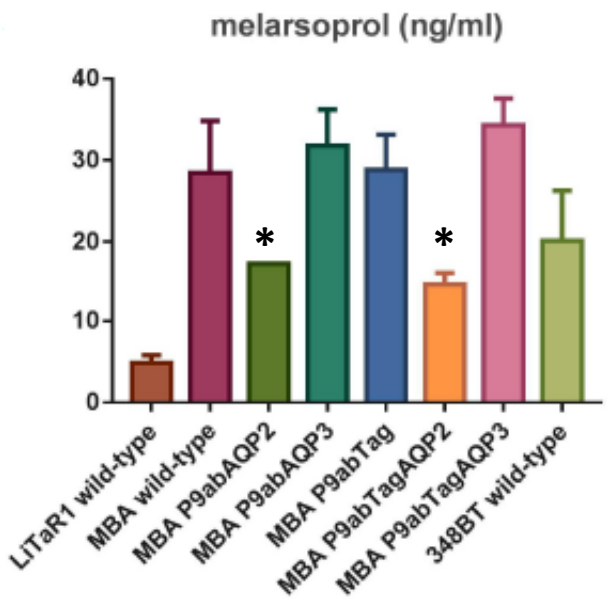
Diversity of *TbgAQPs…*



- Field isolates of *T.b. gambiense* from the Democratic Republic of Congo harbour different *TbAQP2/3* chimaera and *TbAT1* genes
- Presence of *TbAQP2/3* chimaera in the infecting strain does not predict melarsoprol treatment failure in individual patients from different HAT foci

…relation to MPXR in *T.b.g.*





***T.b. gambiense* LiTaR1**

- wild-type *TbAQP2*
- wild-type *TbAT1*
- difficult to transfect
- acute *in vivo* phenotype
- mel & pen sensitive

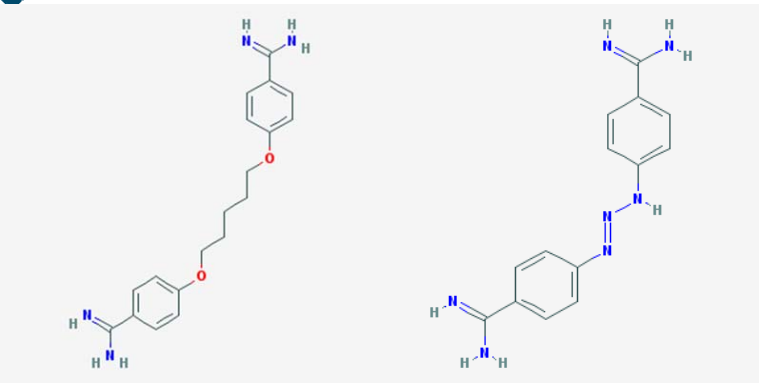
***T.b. gambiense* MBA**

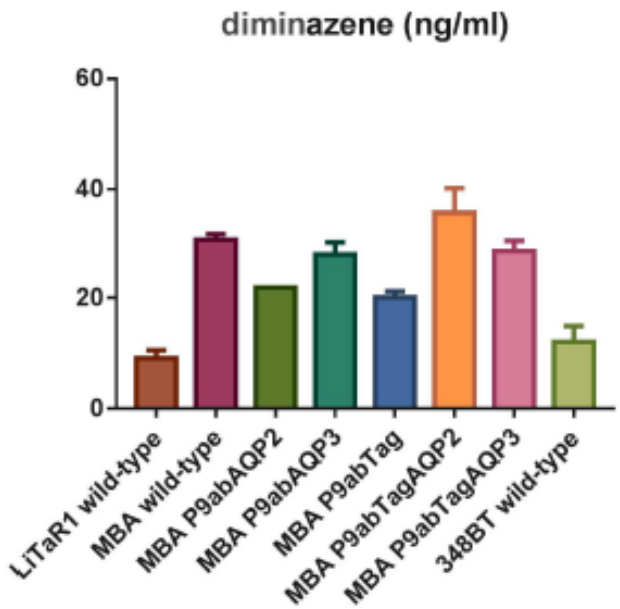
- *TbAQP2/3* chimaera from Bandundu
- Codon deletion in TbAT1$_{(\Delta 516\text{-}518)}$
- difficult to transfect
- subchronic *in vivo* phenotype
- MPXR

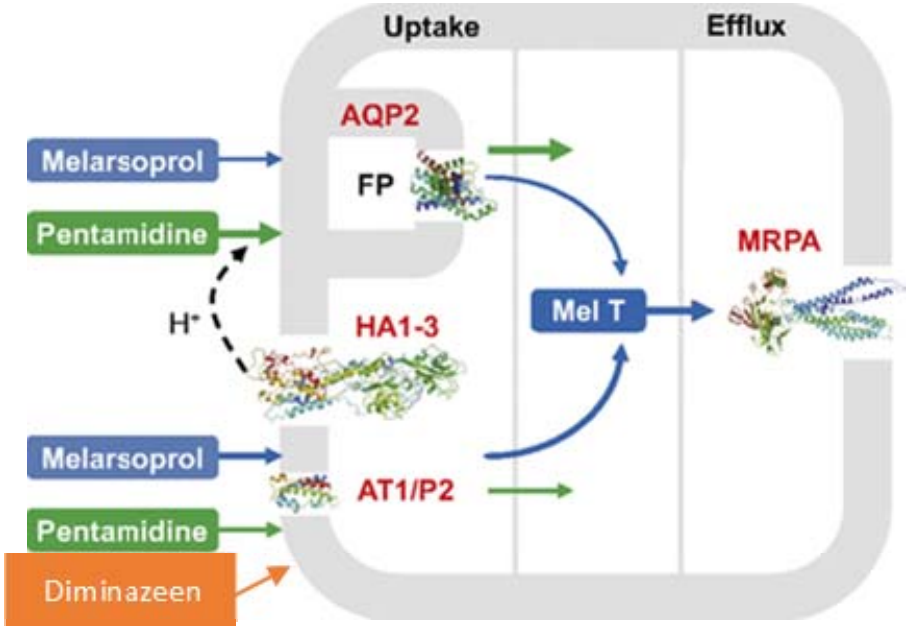
***T.b. gambiense* 348BT**

- *TbAQP2/3* chimaera from Mbuji-Mayi
- wild-type *TbAT1*
- hard to transfect
- chronic *in vivo* phenotype
- MPXR

pentamidine vs diminazene

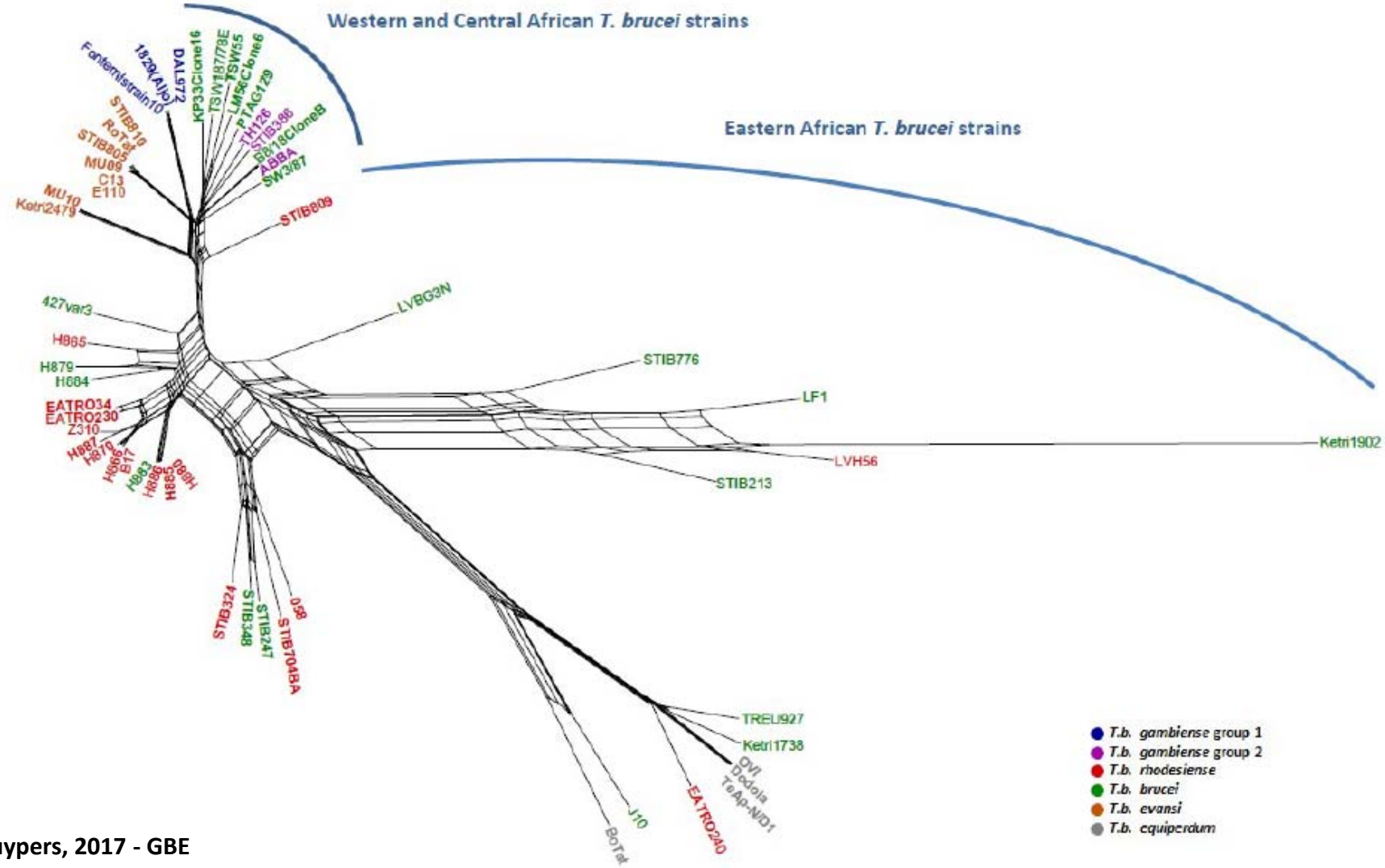






modified from Baker, 2012 - PNAS

Diversity of Trypanozoon



Cuypers, 2017 - GBE

Epidemiology of AQPchi in T. ev/eq

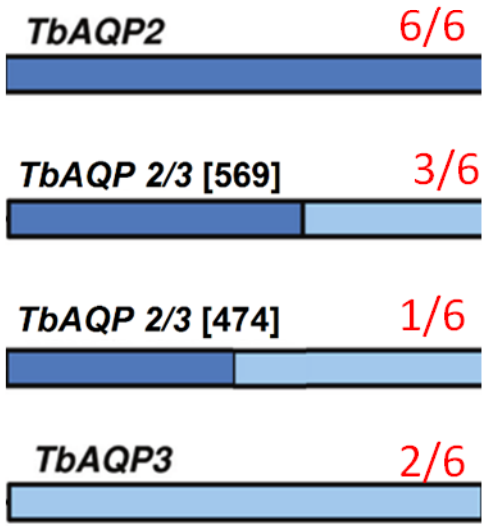
Direct screening of TeAQP2-AQP3 locus (Graf, 2013) revealed modified locus in

***T. equiperdum* ALFORT**	**unknown**	
***T. equiperdum* AnTat 4/1**	**unknown**	
***T. equiperdum* SVP**	**unknown**	
***T. equiperdum* HAMBURG**	**unknown**	
***T. evansi* ZAGORA I.17**	**Morocco**	**Camel**
***T. evansi* AnTat 3/3**	**South America**	**Capybara**
***T. evansi* CAN86K**	**Brazil**	**Dog**
***T. evansi* Merzouga 56**	**Morocco**	**Camel**
***T. evansi* STIB 816**	**PR China**	**Camel**
***T. equiperdum* STIB 818**	**PR China**	**Horse**

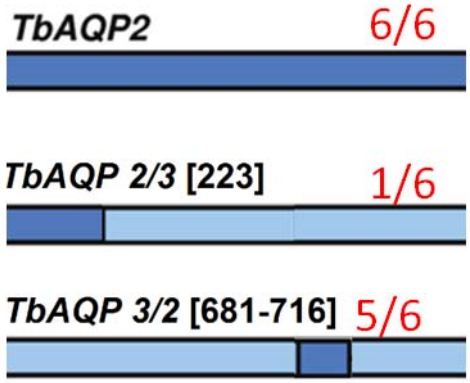
- **Present in strains from Northern Africa, South America and Asia!**
- **<u>Many other *T. evansi* and *T. equiperdum* do not show alterations in this locus.</u>**

Diversity in *TevAQP* and *TeqAQP*…

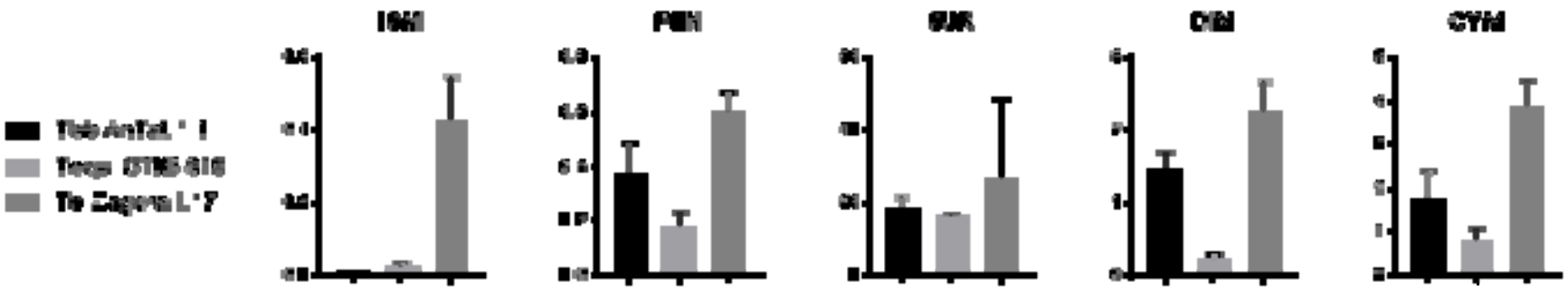
***T. equiperdum* STIB 818 (PRC)**



***T. evansi* ZAGORA I.17 (Morocco)**
***T. evansi* MERZOUGHA 56 (Morocco)**
***T. evansi* STIB 816 (PRC)**



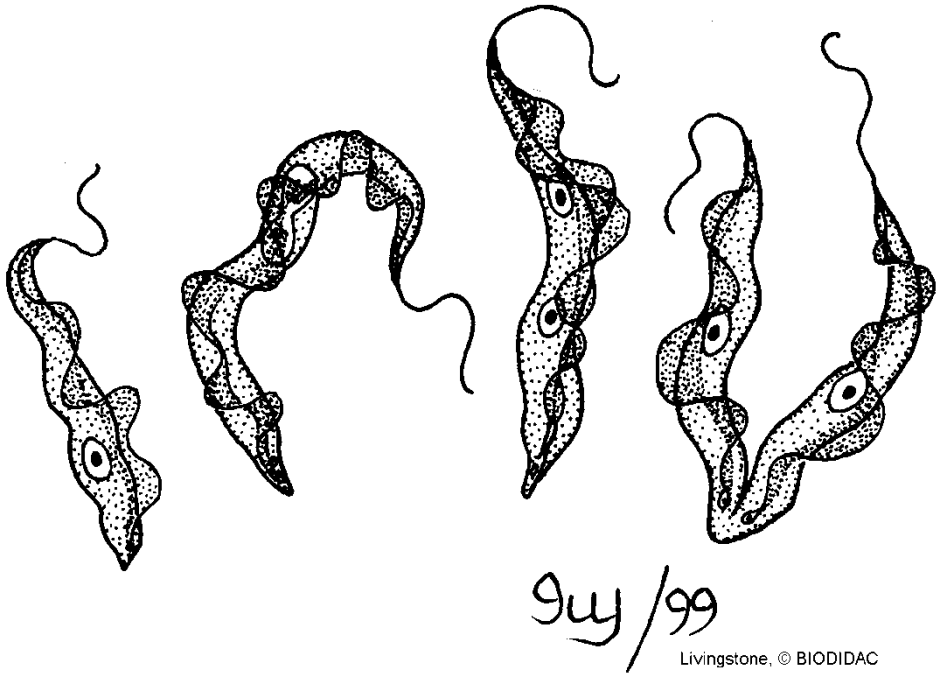
...MPXR in *T. evansi/equiperdum*?



- **No MPXR phenotype found in tested *T. evansi* and *T. equiperdum* strains**
- **Novel Tev and TeqAQP chimera do not cause MPXR: "cryptic" resistance?**

Treatment of Moroccan camels with cymelarsan!
Atarhouch et al 2003, Vet Parasitol
Rami et al 2003, Vet Parasitol

Conclusions

- AQP chimera in *T.b. gambiense*
  - more diversity than expected in *T.b. gambiense* from RDC
  - strains have various degrees of MPXR, likely depended on chimerisation
  - if AQP2 is still present, no MPXR
- AQP chimera in *T. evansi* and *T. equiperdum*
  - strains that are **not treated** with **pentamidine**
  - despite being similar to *Tbb/Tbg* MPXR alleles!
  - **no effect on MPXR**, likely due to presence of wild-type *AQP2*
  - emerged **at least 2** times (*T. equiperdum* STIB 818 vs other strains *)
  - unknown if true MPXR *T. evansi/ T. equiperdum* exist
  - careful with **cymelarsan treatments**?
  - **next challenge is to induced MPXR resistance in these AQPchi strains**

Acknowledgements