Novel molecular mechanism for targeting the parasite Trypanosoma brucei with snake venom toxins

Martos Esteban, Andrea; Laustsen, Andreas Hougaard; Carrington, Mark

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

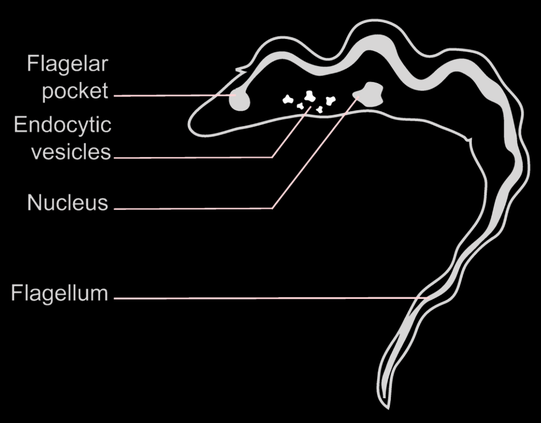
Novel molecular mechanism for targeting the parasite *Trypanosoma brucei* with snake venom toxins

Andrea Martos Esteban[1], Andreas Hougaard Laustsen [1,2], Mark Carrington [3]

[1]Department of Biotechnology and Biomedicine, Technical University of Denmark
[2]Department of Drug Design and Pharmacology, University of Copenhagen
[3]Department of Biochemistry, University of Cambridge

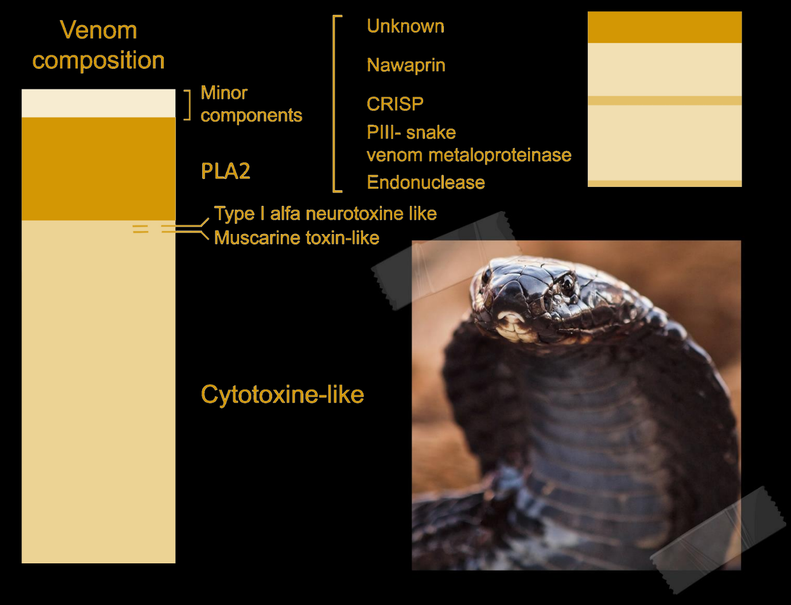
Sleeping sickness: a neglected tropical disease

Trypanosoma brucei is a parasitic protozoan species capable to infecting insect vectors whose bite further produces African sleeping sickness in human beings[1]. During parasites' extracellular lives in the mammalian host, its outer coat, mainly composed of Variable surface glycoproteins (VSGs)[2], undergoes enormous variation in its composition to avoid the host's lytic immunogenic[3].



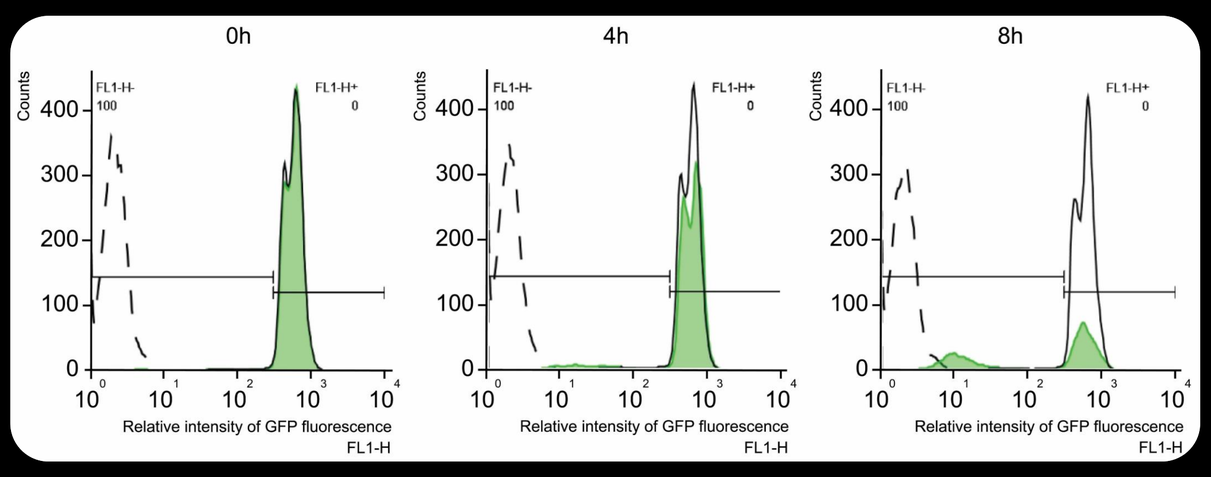
A tropical tale of trypanosomes and snakes

The elapid *N. nigricollis* is a venomous snake (Tanzania)[4]. Since the origins of Pharma, venoms were used as medicines as its toxins target a myriad of different physiological processes with high specificity and selectivity.



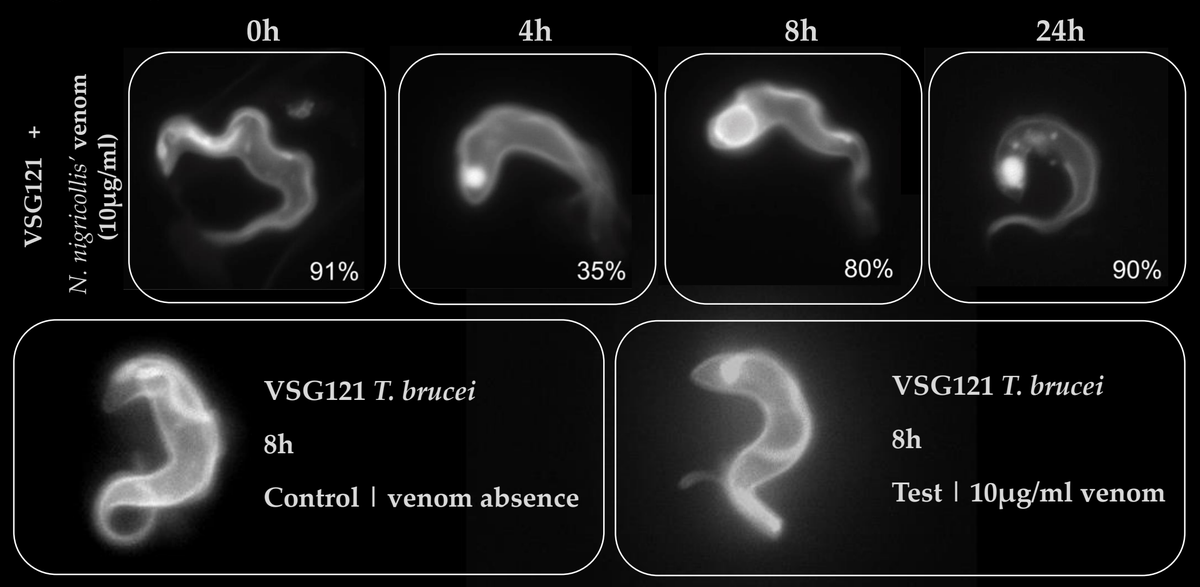
N. nigricollis venom is able to kill *T. brucei* by targeting GPI anchoring of VSG

N. nigricollis' phospholipase A2, one of the major enzymatically active components, could be targeting the GPI anchor of VSG. The lyophilized powder venom was diluted in HMI-9 cell culture media. We cultured *T. brucei* parasites expressing eGFP attached to GPI (VSG121) with 10µm/ml of *N. nigricollis* venom during 24 hours. Then, by flow cytometry, we study the surveillance and the GFP-GPI release.



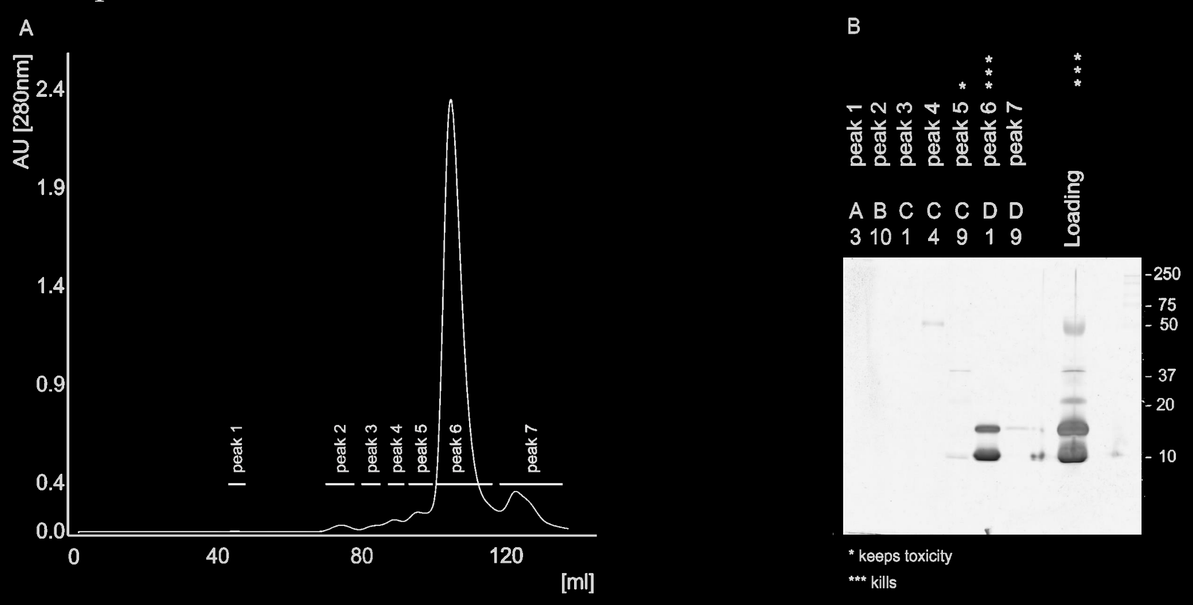
N. nigricollis venom provokes the flagellar pocket enlargement by accumulating GPI

We observed VSG121 parasites using the fluorescence microscope. Contrarily to the parasites' phenotype during venom absence, parasites cultured with the *N. nigricollis* venom show a greener and enlarged flagellar pocket over the time.



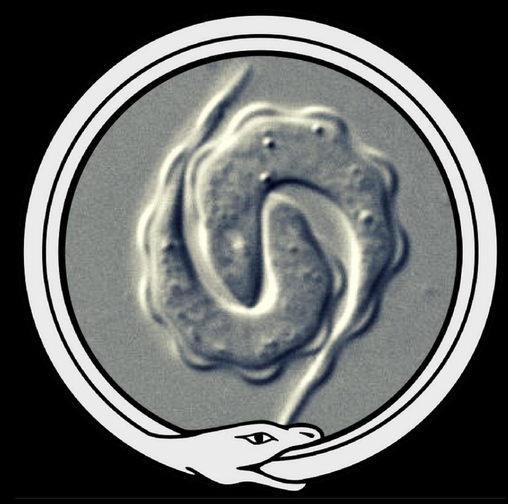
PLA2 and cytotoxines are potentially the toxins responsible of the parasite death

After gel-filtering 20mg of *N. nigricollis* lyophilized venom, we tested each peak in culture and run a SDS PAGE further silver-stained.



Impact

I. First report of using snake venom to effectively kill effectively *T. brucei*.



II. Novel molecular target antigenic variation-independent, allowing to bypass the main inconvenience to develop a successful treatment for the still-today neglected sleeping sickness disease.

III. New therapeutic window, **unveiling the mechanism of parasite lethality that** may help pave the way for novel molecular tools for drug discovery against trypanosome related diseases.

References

[1] Kennedy PGE, 2013. DOI:10.1016/S1474-4422(12)70296-X.
[2] Sunter J, et al. 2013. DOI:10.1371/journal.ppat.1003566.
[3] Fenn K and Matthews KR, 2007. DOI:10.1016/j.mib.2007.09.014.
[4] Petras, D, et al . 2011. DOI:10.1021/pr101040f

Contact information

DTU Bioengeering
Technical University of Denmark
Søltofts Plads 223 - DK-2800 Kgs. Lyngby, Denmark
andrea.martos.esteban@gmail.com / (+34) 676 181 350

Acknowledgements

We thank the Novo Nordisk Foundation (NNF16OC0019248), Symphogen A/S and Otto Monsted Fond for financial support. for financial support.