A Midsummer Night's Sleep. Potential *Trypanosoma brucei* ATP Synthase Inhibitors

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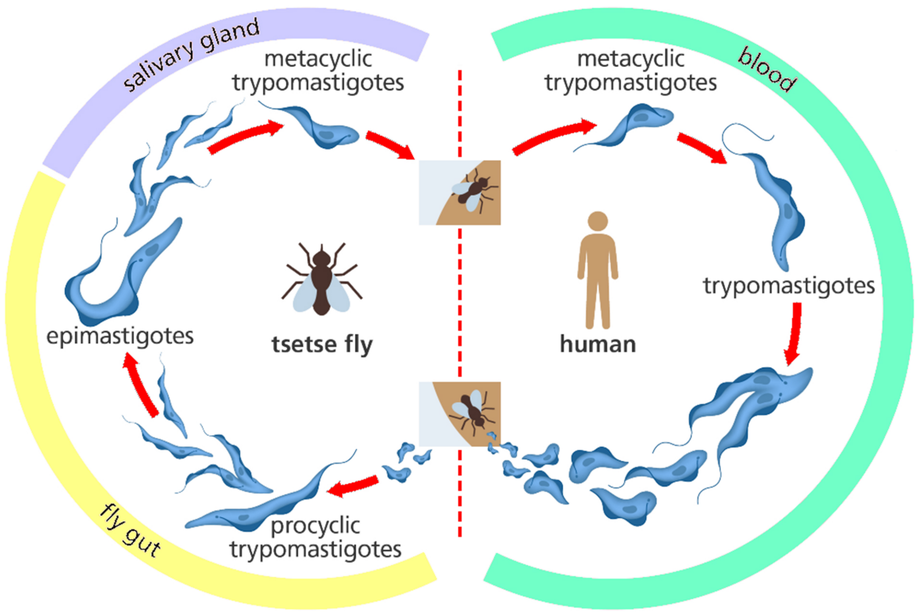
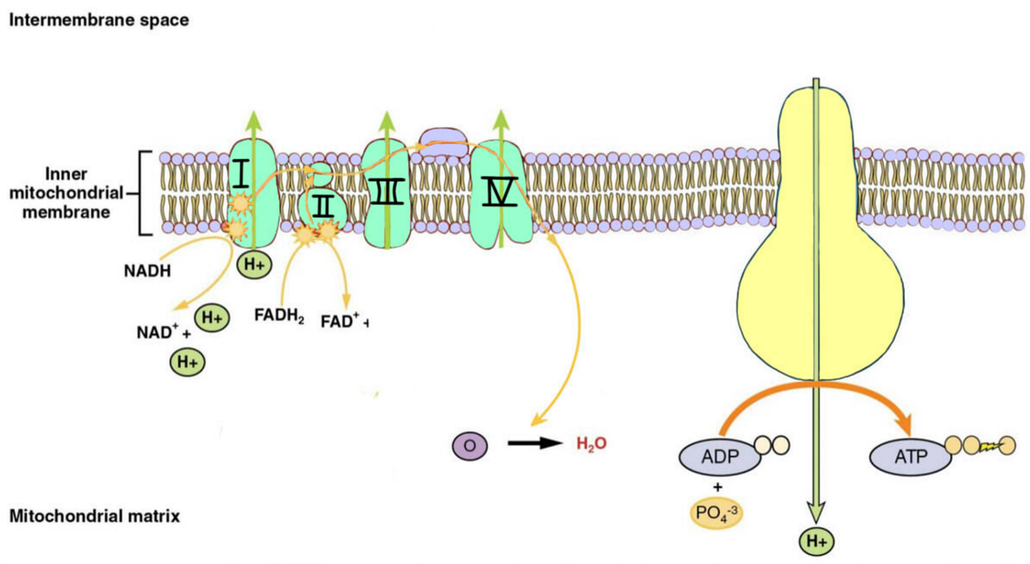
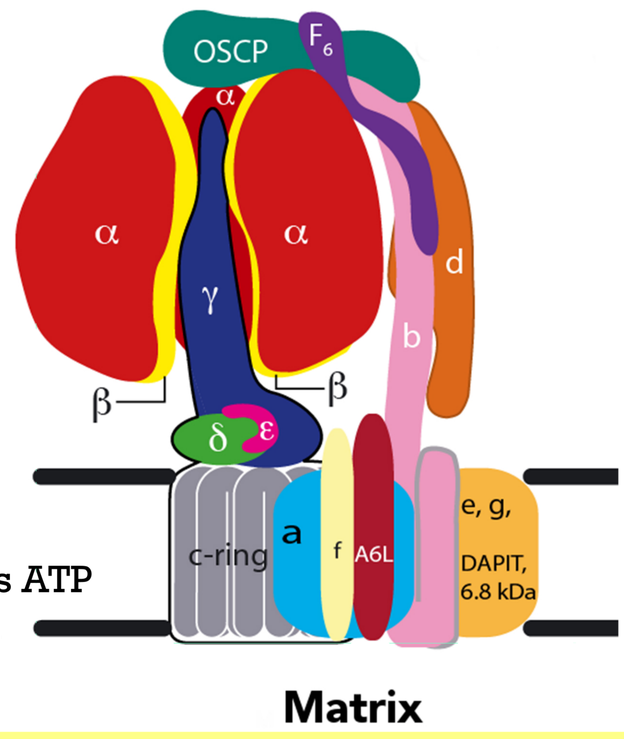
Introduction

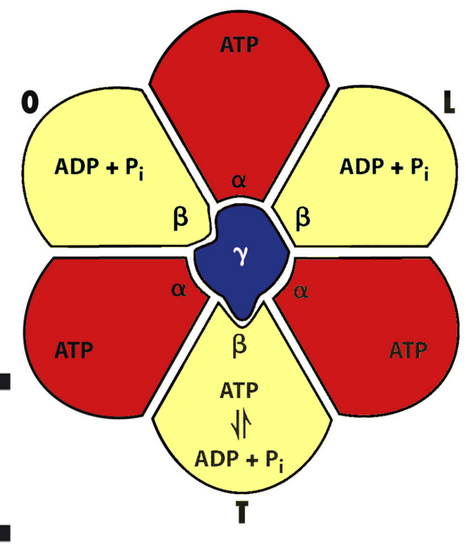
Neglected Tropical Deseases (NTDs) is defined by World Health Organisation as a prioritized claster of infections.
One of the most infamous African diseases is sleeping sickness. It is caused by *Trypanosoma brucei* which is transmitted by tsetse flies.

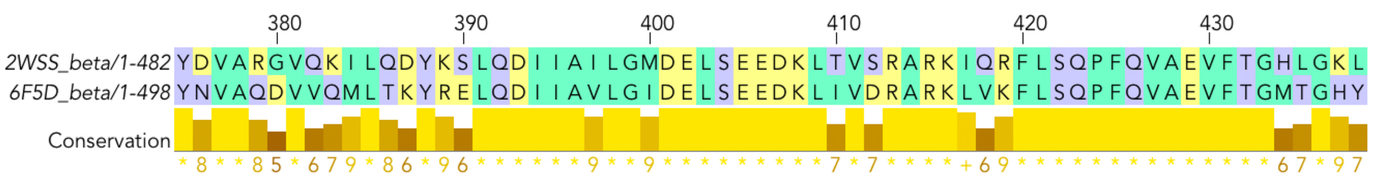




Trypanosoma's ATP synthase in the bloodstream form hydrolyses ATP which drives proton translocation across the inner mitochondrial membrane to maintain the electrochemical proton gradient.



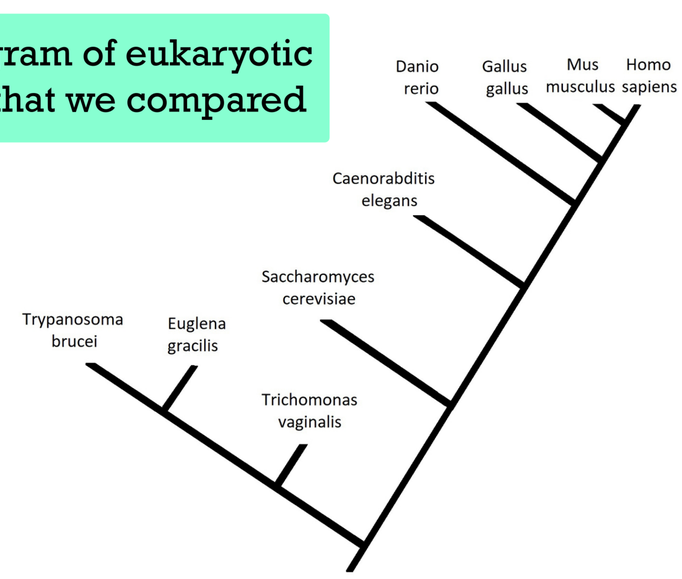


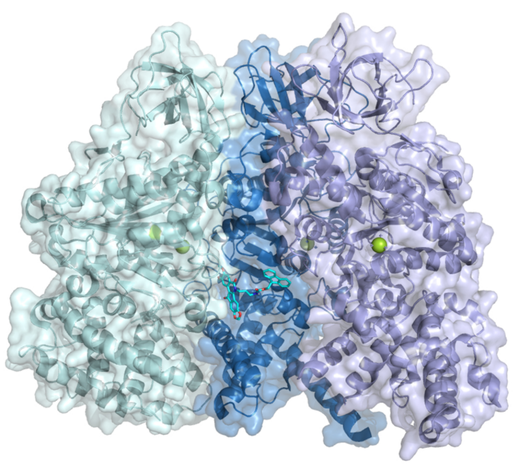


Human and trypanosomal ATP-s sequences alignment

Since Trypanosoma's ATP synthase reverse functioning is essential for the bloodstream form survival, we realised that it is a very promising target and decided to find potent ligands that would block the ATP hydrolysis. We have compared *B. taurus* and *T. brucei* ATP synthase sequences to find a potential binding site for a small molecule.

Cladogram of eukaryotic ATP-s that we compared





Conclusions

	Bos taurus	*Trypanosoma brucei*
NCI_11215802	-6.1	-9.9
NCI_361325	-6.3	-9.9
NCI_361884	-5.5	-9.0
NCI_276180	-6.7	-9.9

Binding energies for the top 4 compounds /

-Vina AutoDock tools package has been used to screen NCI compound set vs target proteins to identify the most prominent inhibitors. Target structures have been taken from Protein Data Bank and have been aligned using TM-Align tool for preliminary analysis and for binding site selection.

- We have found a small molecule with sufficient binding energy difference for the trypanosoma and bovine ATP synthases

- These compounds can be obtained for free via the Developmental Therapeutics Program from National Cancer Institute to be tested experimentally.

References

1. Montgomery M, Gahura O, Leslie A, Zíková A, Walker J. ATP synthase fromTrypanosoma bruceihas an elaborated canonical F1-domain and conventional catalytic sites. Proceedings of the National Academy of Sciences. 2018;115(9):2102-2107.
2. Dewar C, MacGregor P, Cooper S, Gould M, Matthews K, Savill N et al. Mitochondrial DNA is critical for longevity and metabolism of transmission stage Trypanosoma brucei. PLOS Pathogens. 2018;14(7):e1007195.
3. Davies K, Kühlbrandt W. Structure of the catalytic F1head of the F1-FoATP synthase from Trypanosoma brucei. Proceedings of the National Academy of Sciences. 2018;115(13):E2906-E2907.
4. Panicucci B, Gahura O, Zíková A. Trypanosoma brucei TbIF1 inhibits the essential F1-ATPase in the infectious form of the parasite. PLOS Neglected Tropical Diseases. 2017;11(4):e0005552.
5. Gahura O, Šubrtová K, Váchová H, Panicucci B, Fearnley I, Harbour M et al. The F1-ATPase from Trypanosoma brucei is elaborated by three copies of an additional p18-subunit. The FEBS Journal. 2017;285(3):614-628.
6. Kolev N, Ramey-Butler K, Cross G, Ullu E, Tschudi C. Developmental Progression to Infectivity in Trypanosoma brucei Triggered by an RNA-Binding Protein. Science. 2012;338(6112):1352-1353.
7. Nicholls D, Ferguson S. Respiratory Chains. Bioenergetics. 2013;:91-157.

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