

Meeting abstract

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Submitochondrial particles from *Saccharomyces cerevisiae* to screen compounds for antiprotozoal activity

Carmen Streicher¹, Gerlinde Wiesenberger², Thomas Rosenau³ and Lars Gille*¹

Address: ¹Department of Natural Sciences; University of Veterinary Medicine Vienna, Austria, ²Max F. Perutz Laboratories, University of Vienna, Austria and ³Department of Chemistry, University of Natural Resources and Applied Life Sciences, Vienna, Austria

Email: Lars Gille* - lars.gille@vu-wien.ac.at

* Corresponding author

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The development of atovaquone (ATQ)-resistant plasmodia strains suggests a need of new drugs for the mitochondrial bc₁ complex as drug target in protozoa. It was the aim of the study to establish a model consisting of submitochondrial particles (SMP) from yeast (mimicking the protozoal drug target) and bovine heart for the screening of compounds. *Saccharomyces cerevisiae* wild-type strains (W303-1A, DBY747) were grown on YPD-media at 30 °C for three days. After harvesting the cells their cell wall was digested by zymolyase and mitochondria were isolated. From these organelles SMP were prepared by sonication. The inhibition of the quinol:cyt c oxidoreductase activity catalyzed by the mitochondrial bc₁ complex of yeast and bovine heart SMP was measured for a nonspecies-specific inhibitor stigmatellin and for the anti-malaria drug ATQ. IC₅₀ values for stigmatellin in both SMP preparations confirmed its nonselectivity while ATQ inhibited the yeast complex activity about 16 times stronger than the activity of bovine heart SMP. This confirms the functionality of yeast SMP as model for protozoa. A new lead structure TMC20 demonstrated an IC₅₀ value of 808 μM and 112 μM in yeast and bovine heart SMP, respectively. This suggests that structural adjustments are required to increase the inhibition in yeast/protozoa. The yeast model in context with yeast strains mimicking mutated protozoa provides an efficient way to develop drugs for ATQ-resistant plasmodia strains.