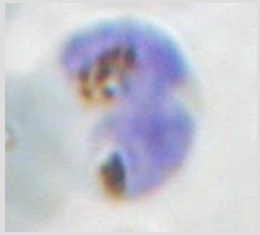

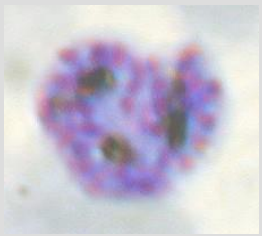

University of São Paulo
Institute of Biomedical Sciences
Department of Parasitology
Unit for Drug Discovery
Carsten Wrenger

Druggability of the Cofactor Metabolism in Malaria

Topics of main interest …..

- Aptamers as diagnostic markers in infectious diseases

  Brazilian-German network between the Universities of São Paulo (USP), Münster (WWU), Hamburg (UHH) and Leipzig

- Oxidative stress control in infectious diseases (helminths and protozoa)

  UNIBRAL partnership INFECTBIO-USP-WWU

- Rational drug design against the plasmodial energy metabolism

  jointly with University of Groningen within MALAR-ASP

- Nuclear receptors in Cancer

  in collaboration with Fraunhofer IME

- Druggability of the cofactor metabolism in malaria and MRSA

  with UHH/DESY, ANU, University of Pretoria

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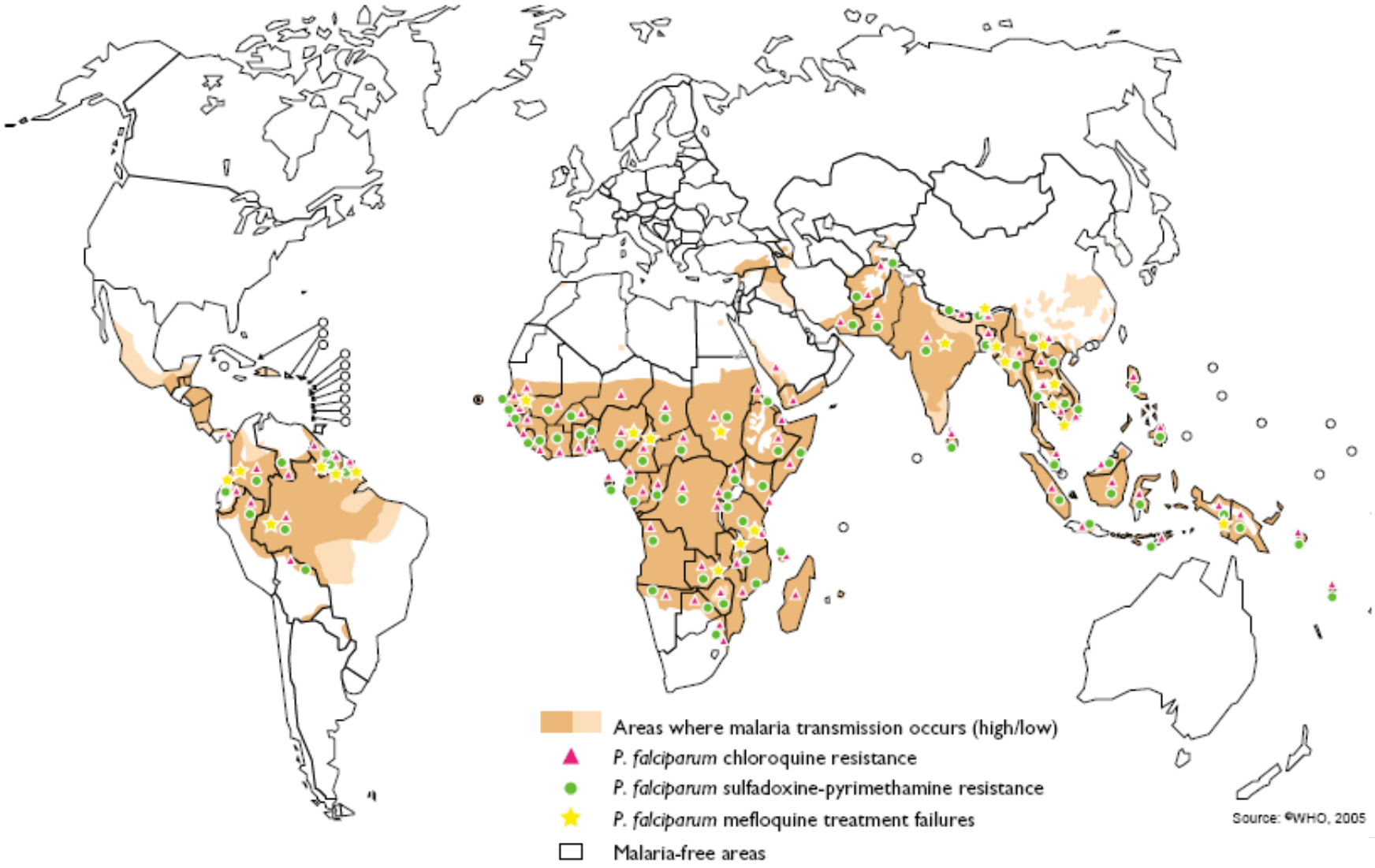
Why do we need novel antimalarials ?



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Development of novel chemotherapeutics

- Chemical agents should be specific for the parasite without affecting the human host

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  - we are focusing on the vitamin B6 metabolism
  - we are also focusing on the vitamin B1 metabolism

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Thiamine pyrophosphate is a cofactor

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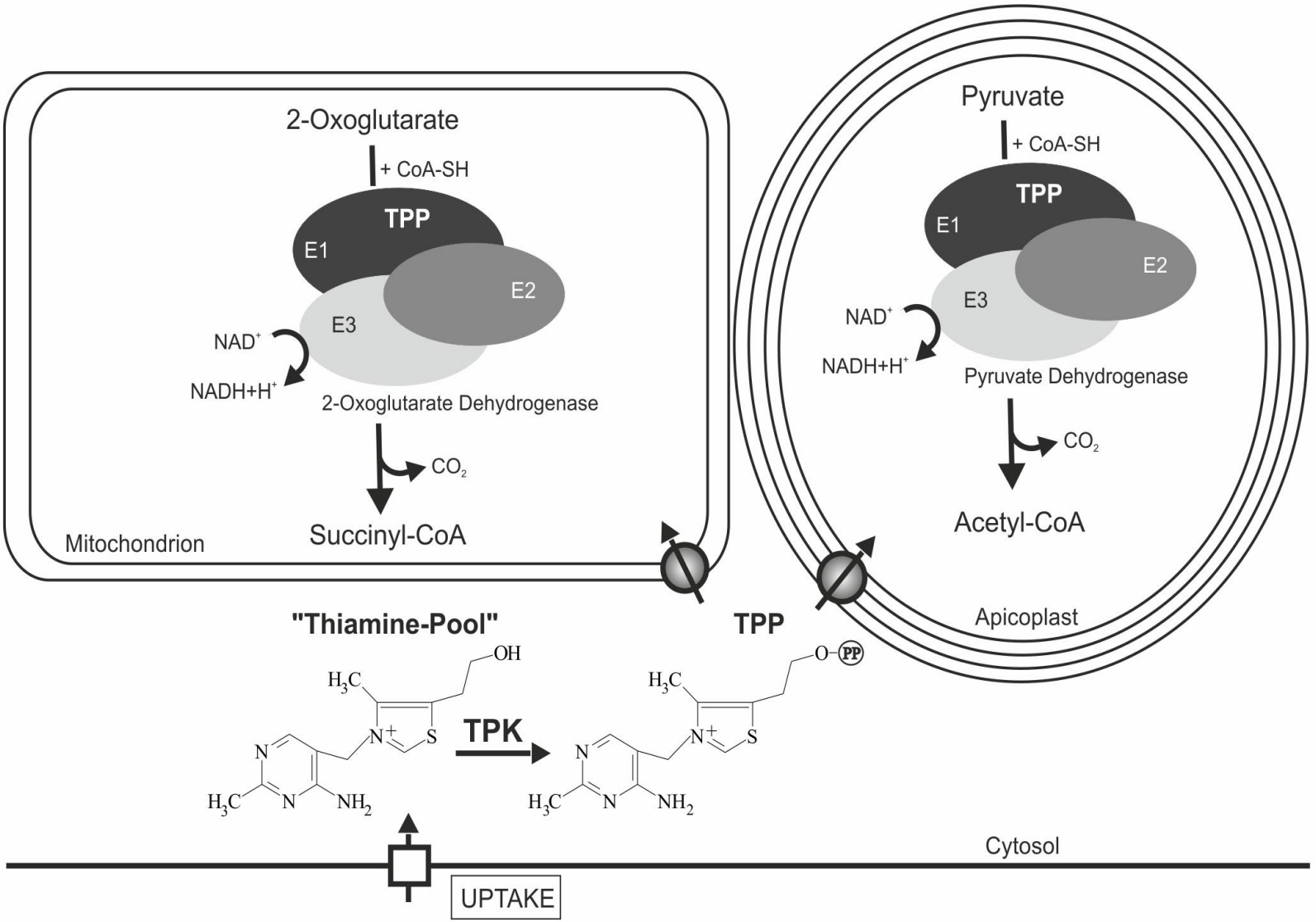
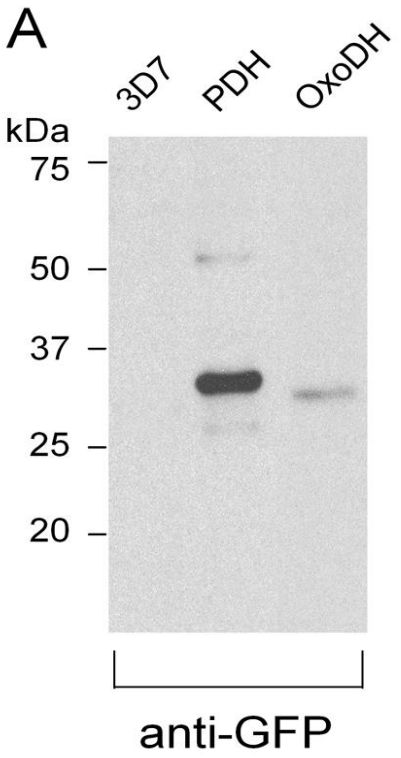


Müller et al., 2010 *Trends Parasitol.*

… in plasmodial organelles



Chan et al., 2013 *Nature Commun*.

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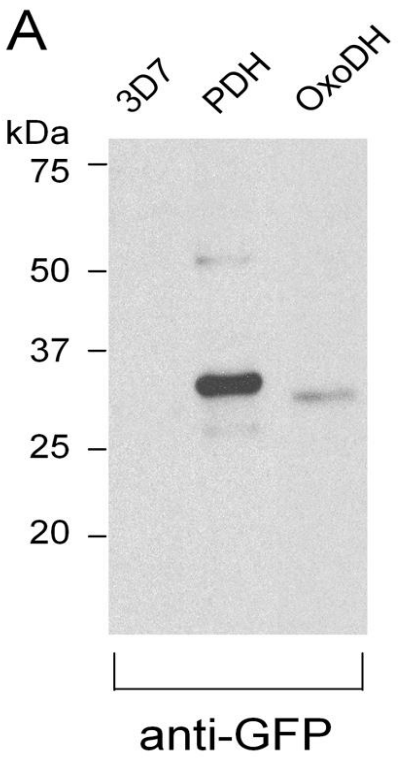
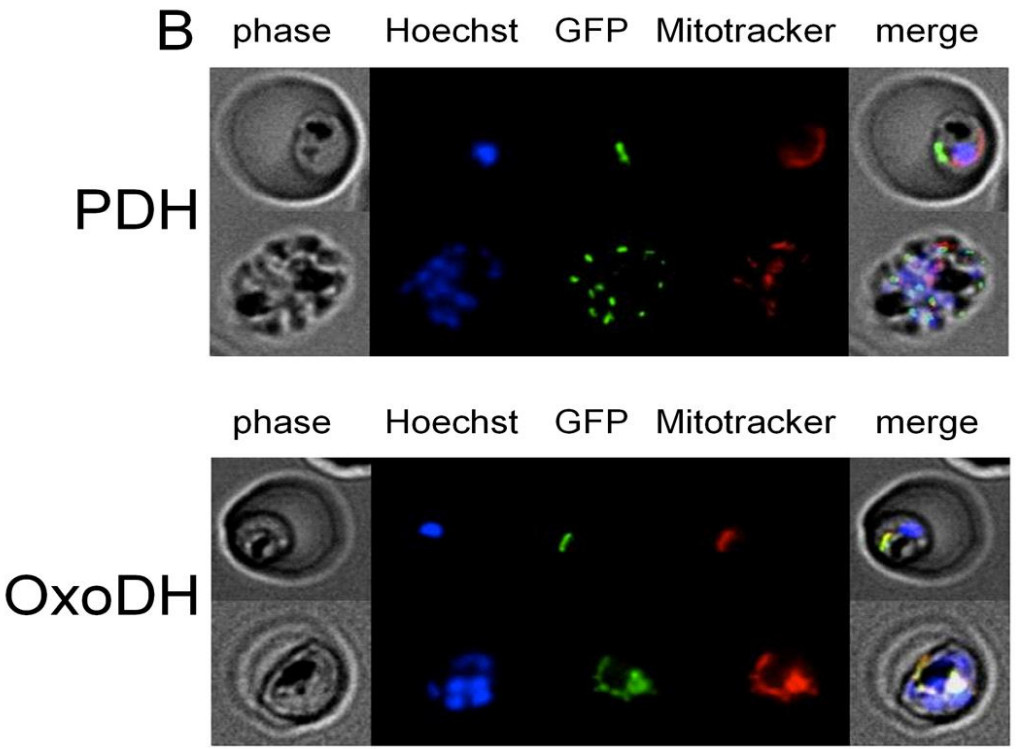
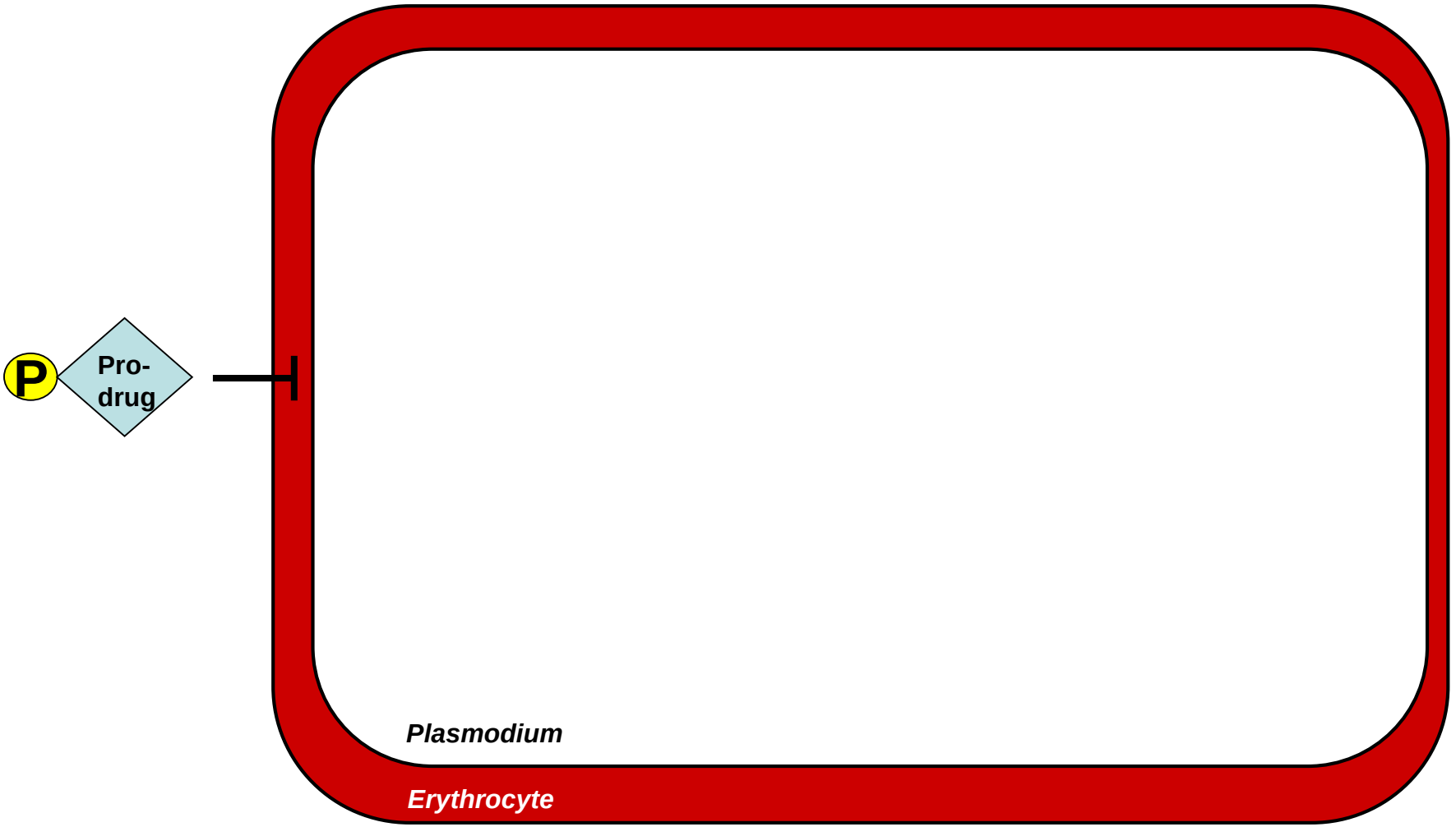




Chan et al., 2013 *Nature Commun*.

Discovery of suicide inhibitors



Drebes et al., 2013 *Curr. Med. Chem.*

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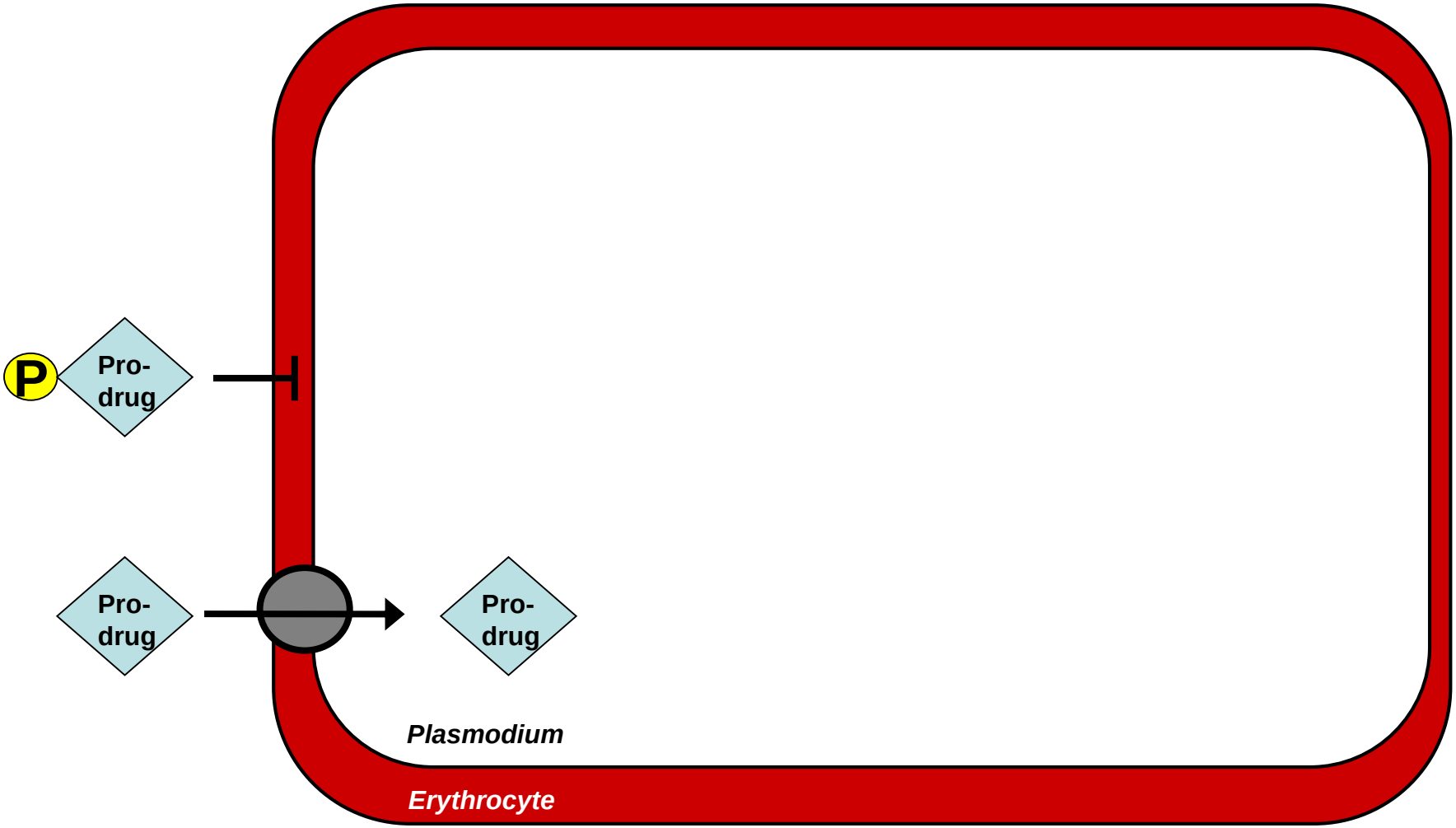
Discovery of suicide inhibitors



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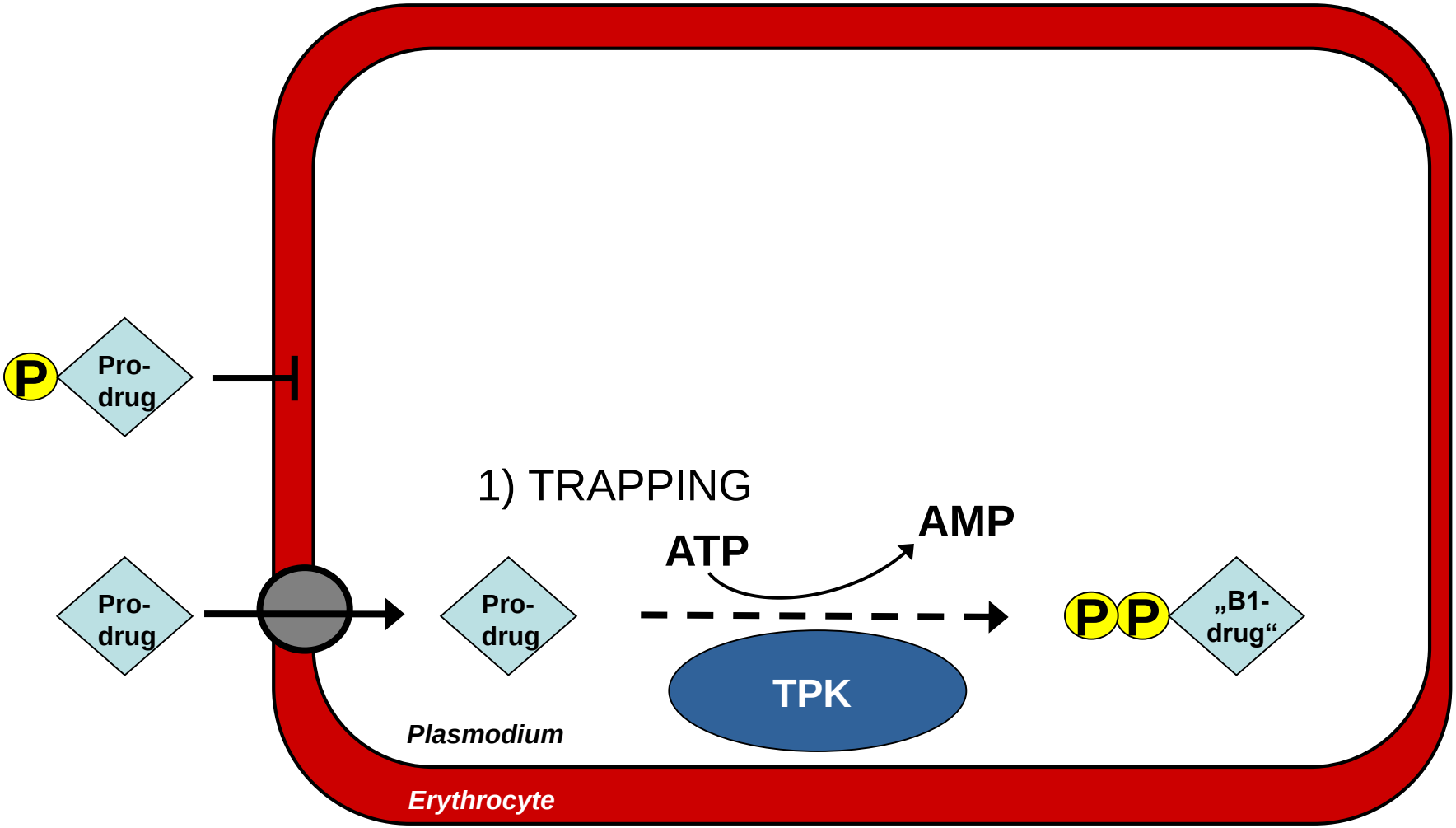

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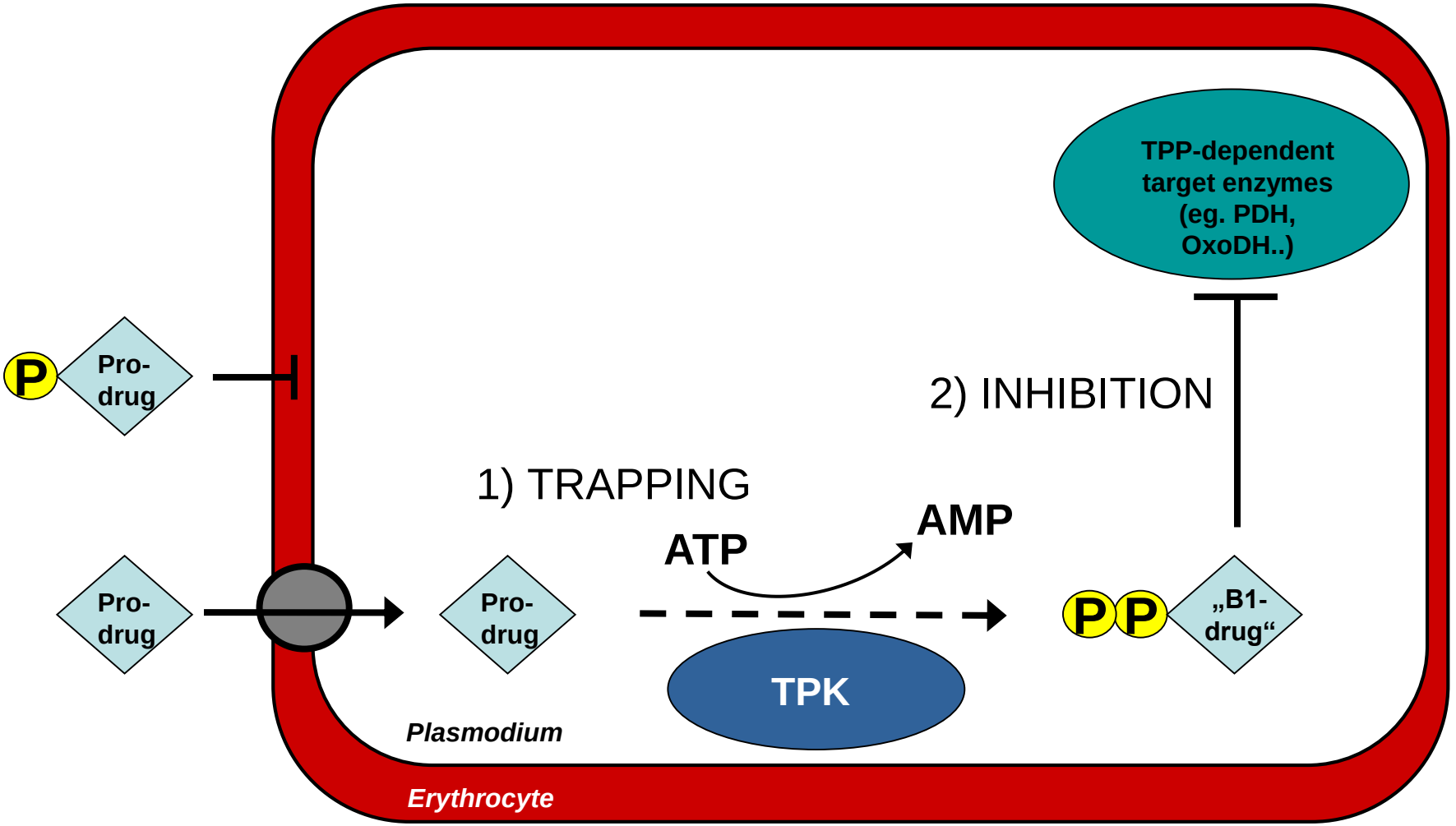

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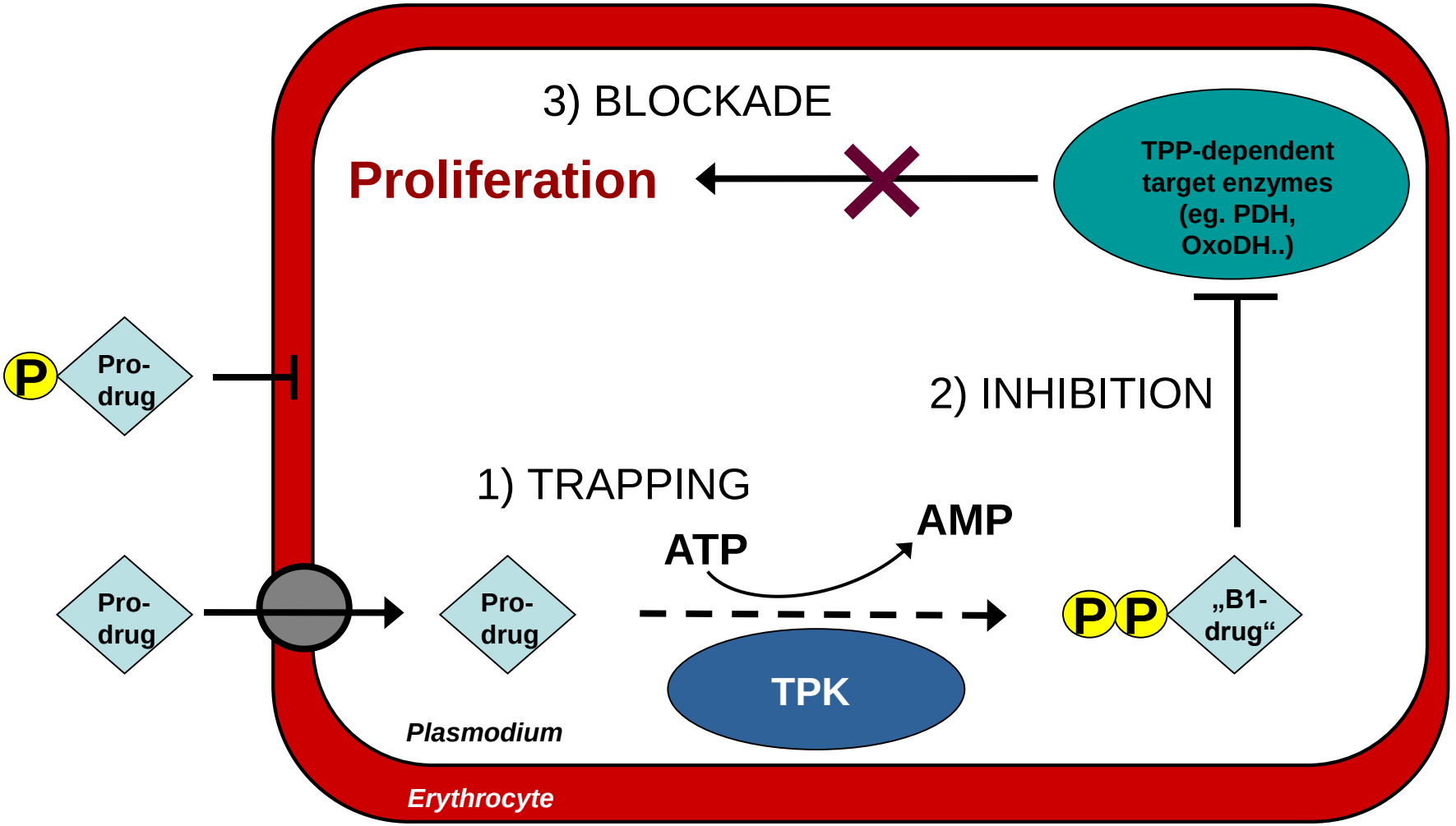

Drebes et al., 2013 *Curr. Med. Chem.*

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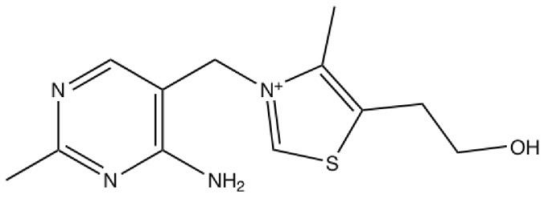
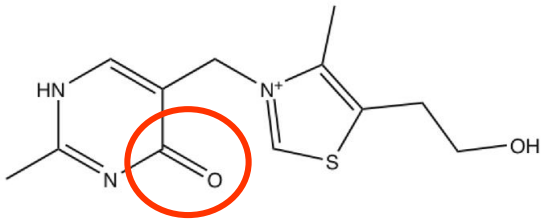
Druggability at the cellular level

A



Thiamine



Oxythiamine

Chan et al., 2013 *Nature Commun*.

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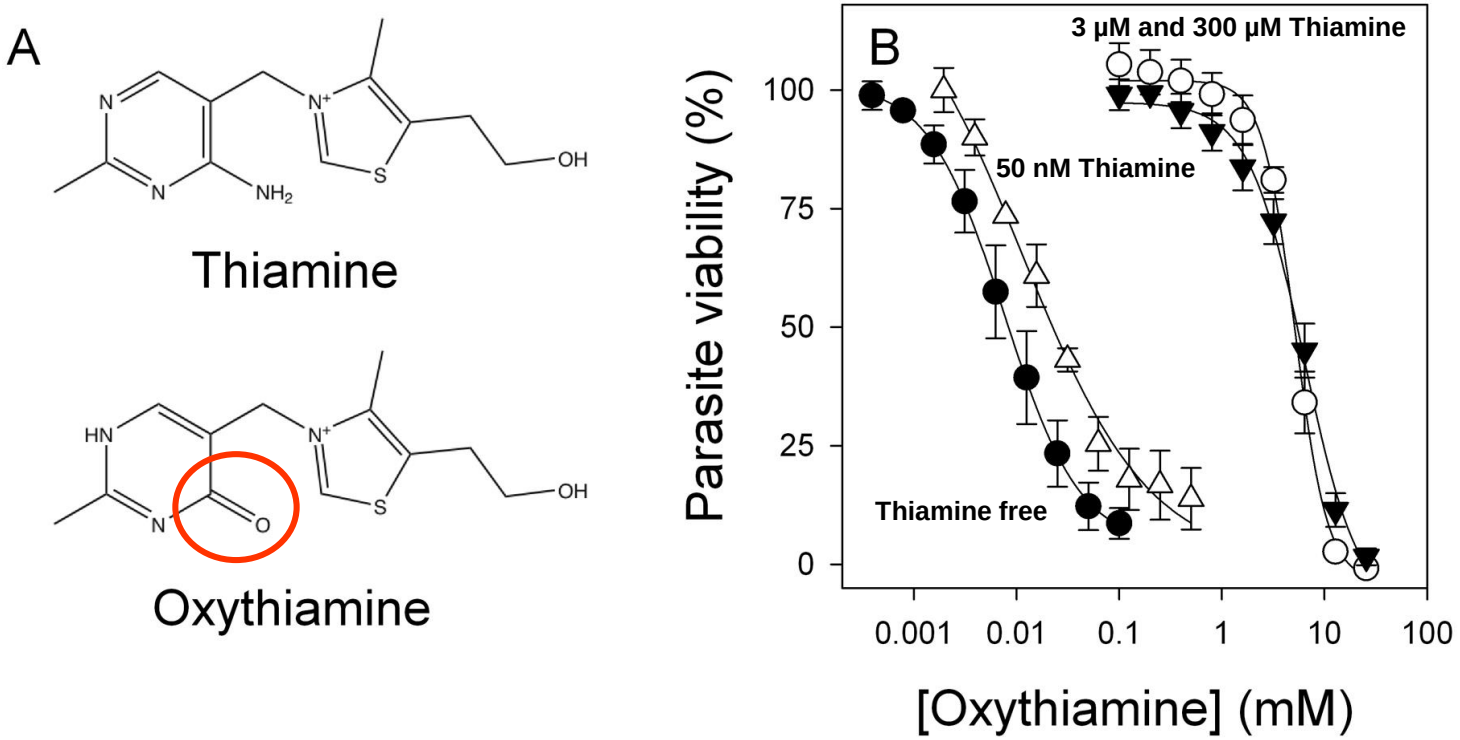
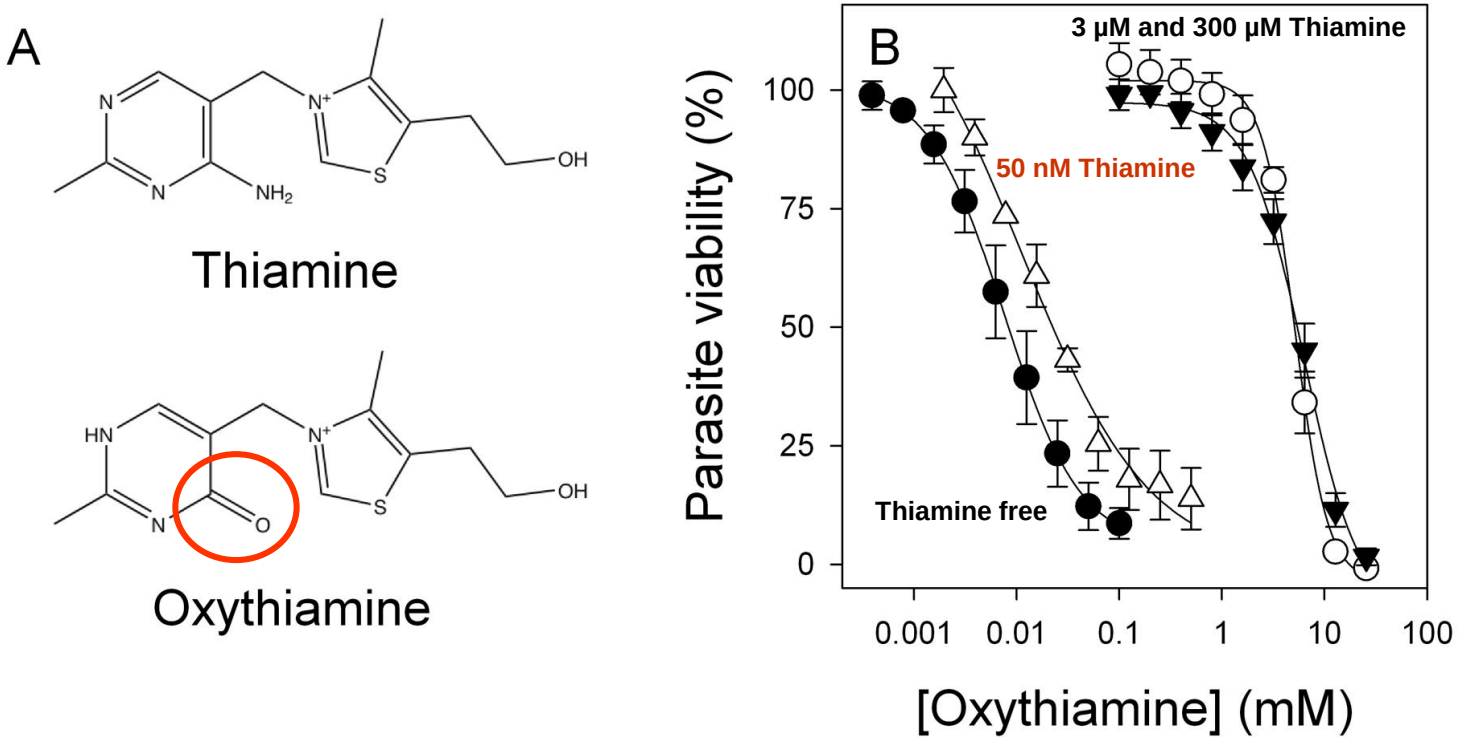
Druggability at the cellular level



Chan et al., 2013 *Nature Commun*.

Druggability at the cellular level



Thiamine concentration in human serum has been determined to be about 7 - 43 nM.

Chan et al., 2013 *Nature Commun*.

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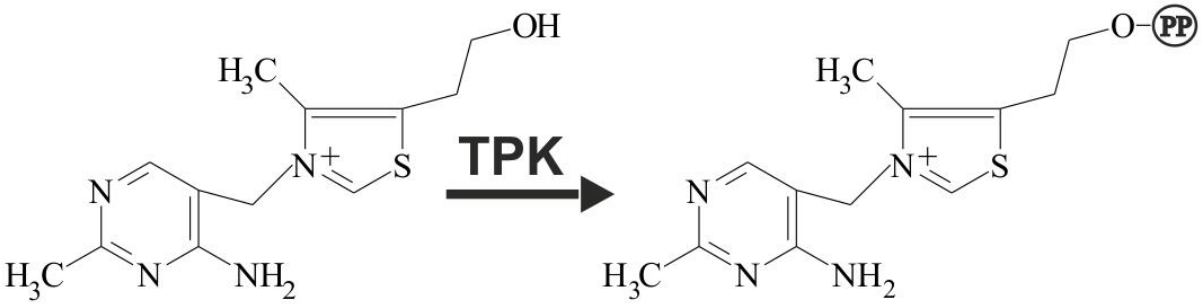
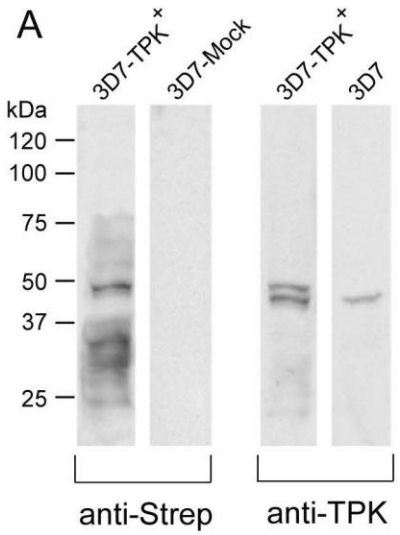
Is the drug accepted by the recombinant TPK?



K_M-value: 76 ± 6 µM

YES!

Is the drug also working at the cellular level?



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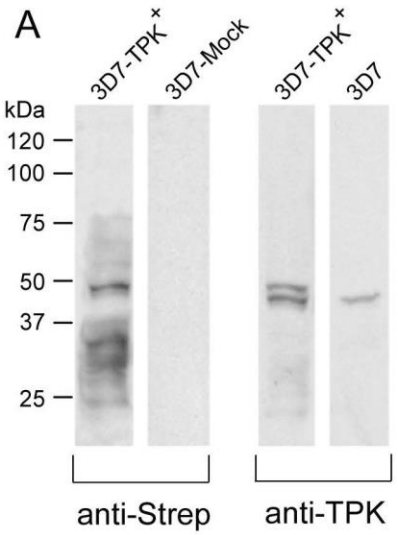

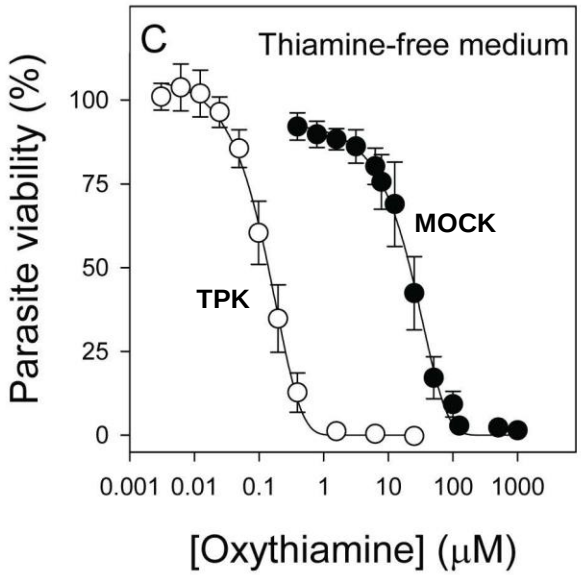

Over-expression of the *Pf*TPK resulted in an

approx. *1000-fold*

***higher sensitivity* to oxythiamine**

YES!

Chan et al., 2013 *Nature Commun*.

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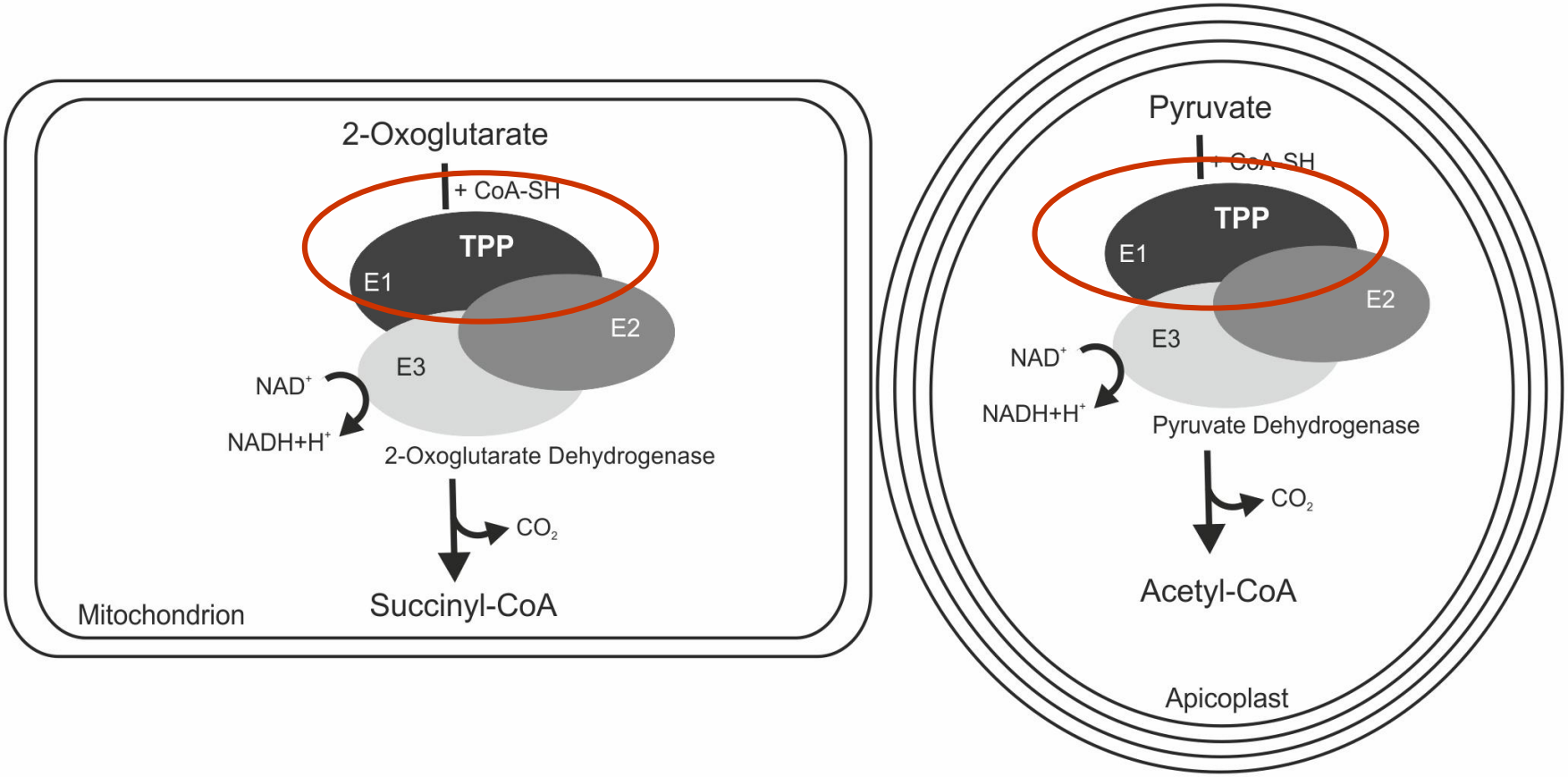
The down-stream effect



Kronenberger et al., 2013 *Future Med. Chem*.

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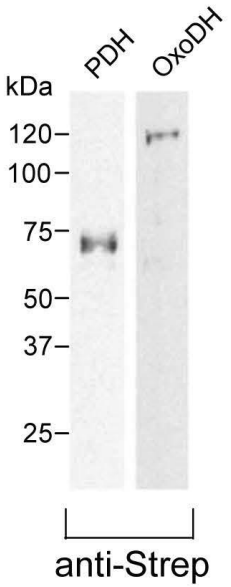
Evaluation of the down-stream effect



Chan et al., 2013 *Nature Commun*.

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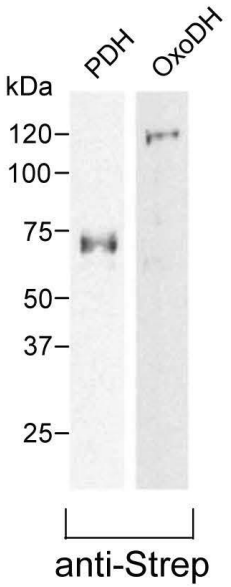

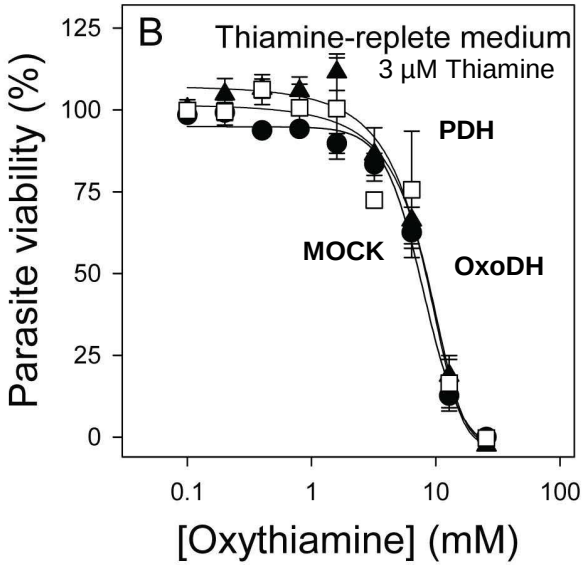

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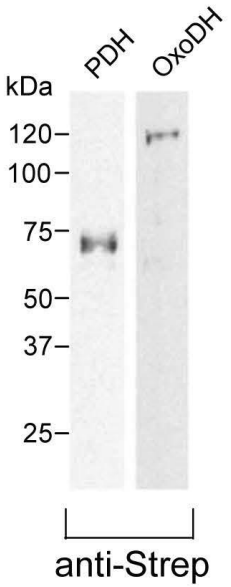

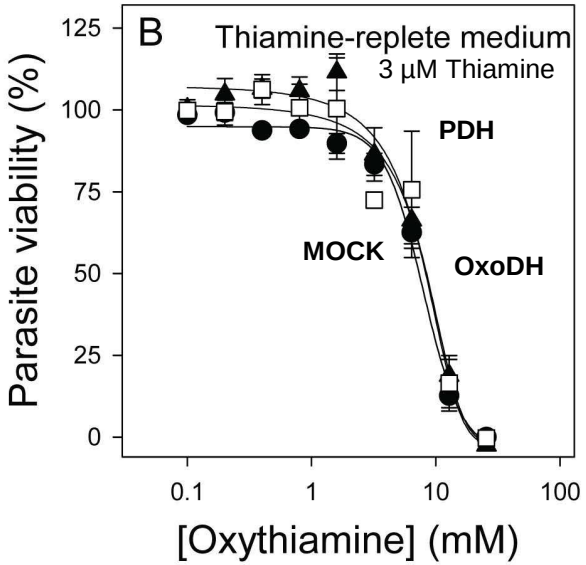

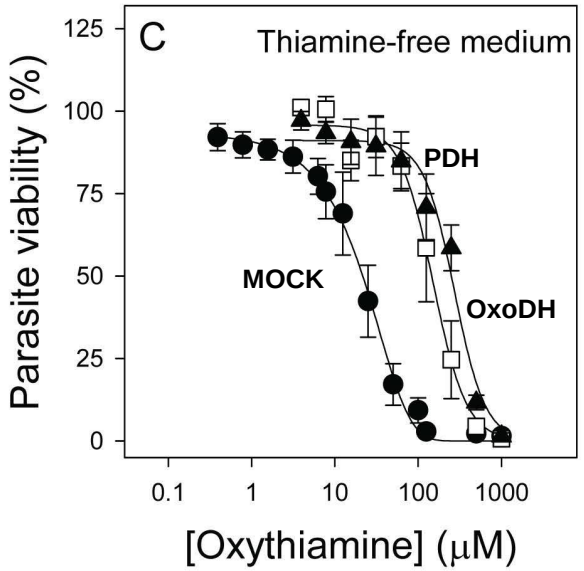

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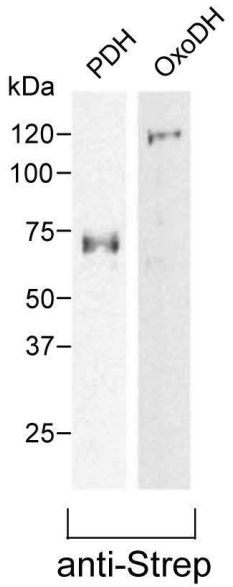

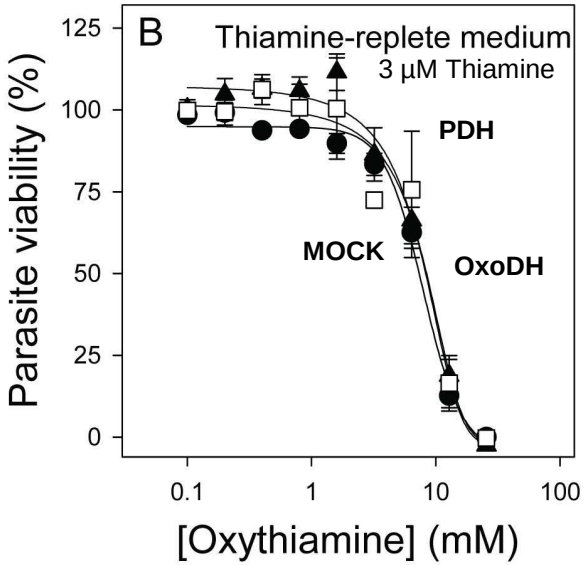

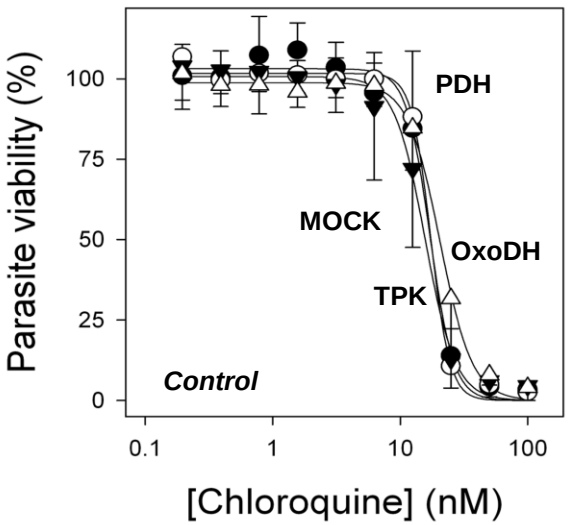

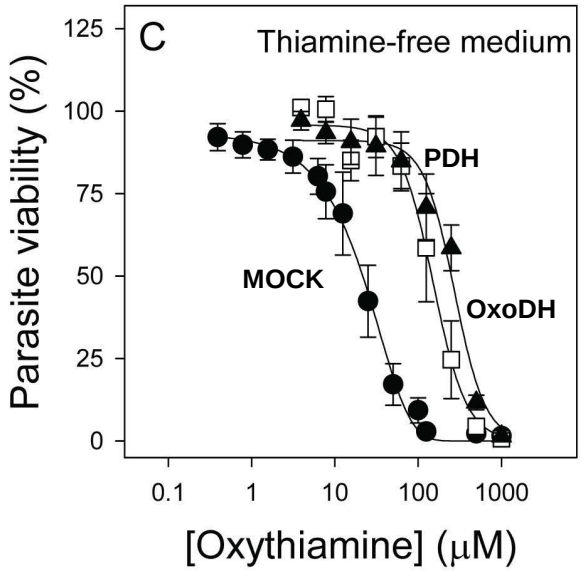

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