Druggability of the Cofactor Metabolism in Malaria
• 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

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Why do we need novel antimalarials?
Development of novel chemotherapeutics

• Chemical agents should be specific for the parasite without affecting the human host
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• “Ideal” drug targets are parasite-specific enzymes which are not present in humans
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  - we are focusing on the vitamin B6 metabolism
  - we are also focusing on the vitamin B1 metabolism
Thiamine pyrophosphate is a cofactor
Thiamine pyrophosphate is a cofactor

Müller et al., 2010 Trends Parasitol.
... in plasmodial organelles

Chan et al., 2013 Nature Commun.
... in plasmodial organelles

Chan et al., 2013 Nature Commun.
Discovery of suicide inhibitors

Plasmodium

Erythrocyte

Pro-drug

Discovery of suicide inhibitors

Discovery of suicide inhibitors

Discovery of suicide inhibitors

Pro-drug

1) TRAPPING

Pro-drug

Pro-drug

Plasmodium

Erythrocyte

TPP-dependent target enzymes (eg. PDH, OxoDH..)

2) INHIBITION

TPK

AMP

ATP

“B1-drug”

Discovery of suicide inhibitors

TPP-dependent target enzymes (eg. PDH, OxoDH..)

1) TRAPPING

2) INHIBITION

3) BLOCKADE

Proliferation

Druggability at the cellular level

In comparison: The thiamine concentration in human serum has been determined to be between 6.6 and 43 nM.

Thiamine free 50 nM Thiamine 3 µM and 300 µM Thiamine

Chan et al., 2013 Nature Commun.
Druggability at the cellular level

The thiamine concentration in human serum has been determined to be between 6.6 and 43 nM.

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.
Is the drug accepted by the recombinant TPK?

Yes!
Is the drug also working at the cellular level?

Chan et al., 2013 Nature Commun.
Is the drug also working at the cellular level?

Over-expression of the PfTPK resulted in an approx. 1000-fold higher sensitivity to oxythiamine

YES!
The down-stream effect

Kronenberger et al., 2013 Future Med. Chem.
Evaluation of the down-stream effect

Chan et al., 2013 Nature Commun.
Evaluation of the down-stream effect

Chan et al., 2013 Nature Commun.
Evaluation of the down-stream effect

B) Thiamine-replete medium
3 µM Thiamine

<table>
<thead>
<tr>
<th>[Oxythiamine] (mM)</th>
<th>Parasite viability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td></td>
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<tr>
<td>1</td>
<td></td>
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<tr>
<td>10</td>
<td></td>
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<tr>
<td>100</td>
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</tbody>
</table>

C) Thiamine-free medium

<table>
<thead>
<tr>
<th>[Oxythiamine] (µM)</th>
<th>Parasite viability (%)</th>
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</tr>
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</table>

Chan et al., 2013 Nature Commun.
Evaluation of the down-stream effect

![Graph](image1.png)

- **Thiamine-replete medium**: 3 µM Thiamine
  - **MOCK**: PDH, OxoDH
  - **Parasite viability (%)** vs **[Oxythiamine] (mM)**

![Graph](image2.png)

- **Thiamine-free medium**: 0.1, 1, 10, 100 nM Chloroquine
  - **Control**: PDH, TPK, OxoDH
  - **Parasite viability (%)** vs **[Chloroquine] (nM)**

![Graph](image3.png)

- **Thiamine-free medium**: 0.1, 1, 10, 100, 1000 µM Oxythiamine
  - **MOCK**: PDH, OxoDH
  - **Parasite viability (%)** vs **[Oxythiamine] (µM)**
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