Potential impact of new drug development

Synthetic Peroxides: A Viable Alternative to Artemisinins

25 June 2007 Bangkok

Curing Malaria Together www.mmv.org

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Role of Artemisinins in the Treatment of Malaria

- Artemisinin derivatives are now the mainstay of treatment for malaria
- Since WHO endorsement of Artemisinin-based Combination Therapy (ACT) as 1st or 2nd line therapy for uncomplicated *P. falciparum* malaria:
  - strategy has been adopted by 69 countries
  - forecast for 2007 of 150 million treatments
- Heavy reliance on the artemisinin component:
  - fast acting, highly effective against both *P. falciparum* and *P. vivax*
  - rapidly cleared; used in combination with a longer-acting partner drug
- But there are issues…
  - supply, cost, natural source
  - any clinical resistance to artemisinin will jeopardize ACT strategies
  - concerns regarding use in some special populations (infants, pregnancy)

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What is MMV

- A not for profit organisation
- Creation of MMV in 1999 by
  - WHO
  - The World Bank
  - Donor governments (CH, UK)
  - Philanthropic foundations
  - IFPMA

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MMV Collaboration Principles

- **MMV's overall objective is to ensure the sustainable and continuous generation of <u>appropriate</u> new malaria medicines that are <u>accessible</u> to those in need in developing countries at the <u>lowest prices practicable</u>.**

- <u>A</u>PPROPRIATE
- <u>A</u>FFORDABLE
- <u>A</u>CCESSIBLE

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Objectives of the Synthetic OZ Project

- First Generation OZ project aimed to:
  - identify a new class of peroxides
  - more potent than the currently available semi-synthetic artemisinin derivatives in reducing parasite burden
  - fully synthetic
  - low cost (< $1 USD per treatment when used in combination)
  - 3 day treatment regimen when used in combination
- Next Generation OZ project extends these goals to also include:
  - provision in combination of a single-dose oral cure for patients with uncomplicated *P. falciparum* malaria (and possibly *P. vivax*)
  - potential for prophylactic treatment and intermittent preventative treatment in pregnant women and infants (IPTp and IPTi)

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First Generation of Synthetic Peroxices

OZ277 or RBx11160

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What do we know about RBx 11160?

- More active than CQ, MF, and artemisinin derivatives against *P. falciparum in vitro*, and *P. berghei* in mice
- Good physicochemical and metabolic profile; good PK and oral bioavailability in rats and dogs; half-life shorter than desired
- Excellent safety profile in rats, dogs and humans after single and repeat administration
- Similar exposure after single and repeat administration in humans; minimal food effects

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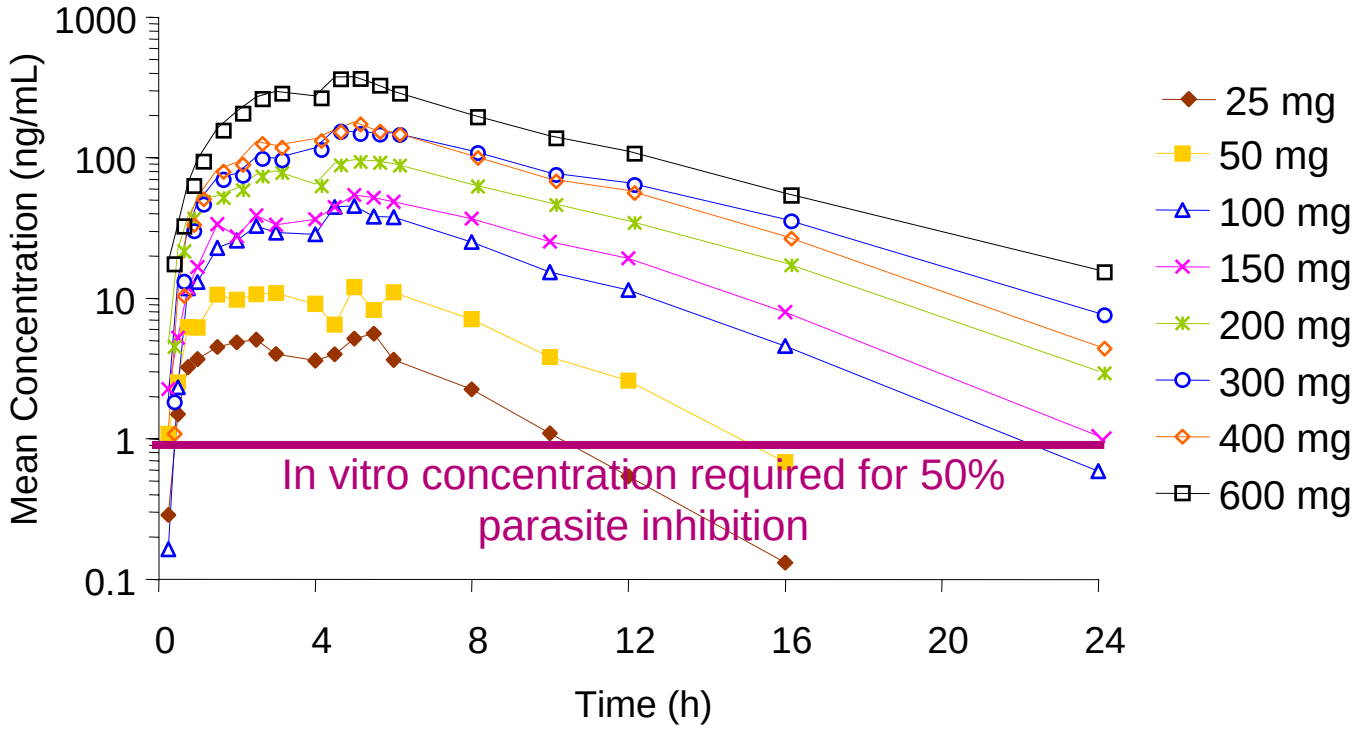
Phase 1 Plasma Concentrations of RBx 11160

Plasma concentrations after a single oral dose to healthy volunteers



- Excellent exposure at doses of 100 mg or above...
- Highly consistent with predictions based on animal data
- But ...

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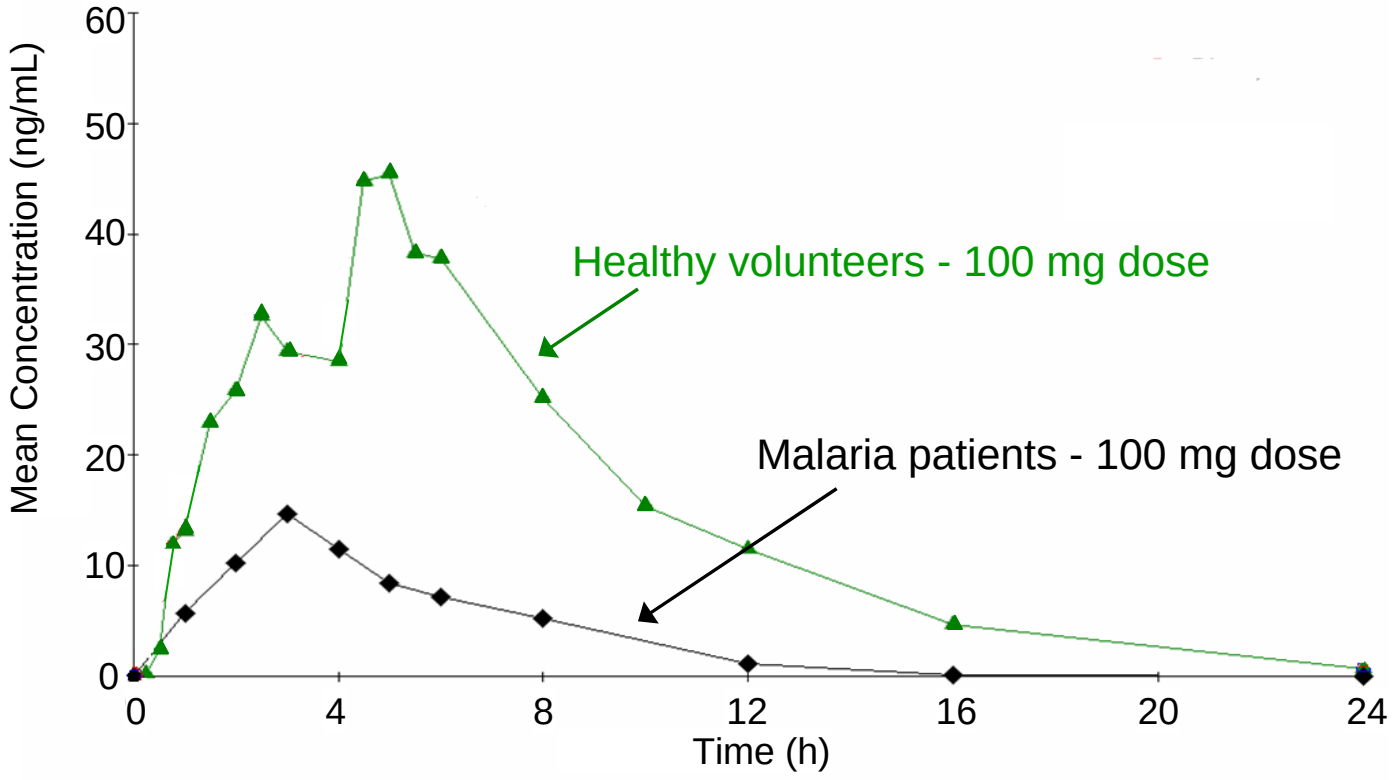
"Issues" that Arose with RBx 11160 in Phase 2



- Significant reduction in plasma concentrations in malaria patients...
- Such reduced exposure meant unlikely to meet 3-day treatment regimen

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Clinical Study MMV05-06 of RBx11160 Monotherapy:

- A Phase II, Dose-Ranging Study with RBx 11160 Administered for 7 Days in 230 Patients With Acute Uncomplicated *Plasmodium falciparum* Malaria was recently concluded.
- Analysis is ongoing
- Early results show that the cure rate (PCR corrected ACPR) is well below MMV's target (90% efficacy) for individual components of a combination product.

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Basis for Reduced Exposure of RBx 11160 in Patients

Possible “first cut” explanations:

- time of dosing — no effect
- postural differences — no effect
- ethnic differences in metabolism — no effect

Differences due to the presence of the infection:

- definition of clearance mechanisms for RBx 11160 (and the resulting affect on plasma concentrations)
- exploration of the blood stability *in vitro* ± parasites

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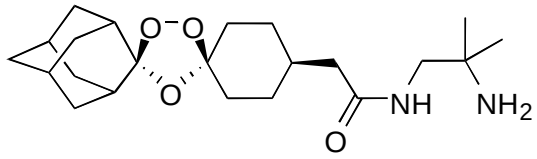
OZ Clearance in Red Blood Cells (RBC)



RBx 11160

Fe(II)
cleavage

inactive cleavage products

- RBC contains haemoglobin - Fe(II) haem
- Cleavage of peroxide by Fe(II)-containing components in RBC
- Cleavage contributes to clearance from the circulation

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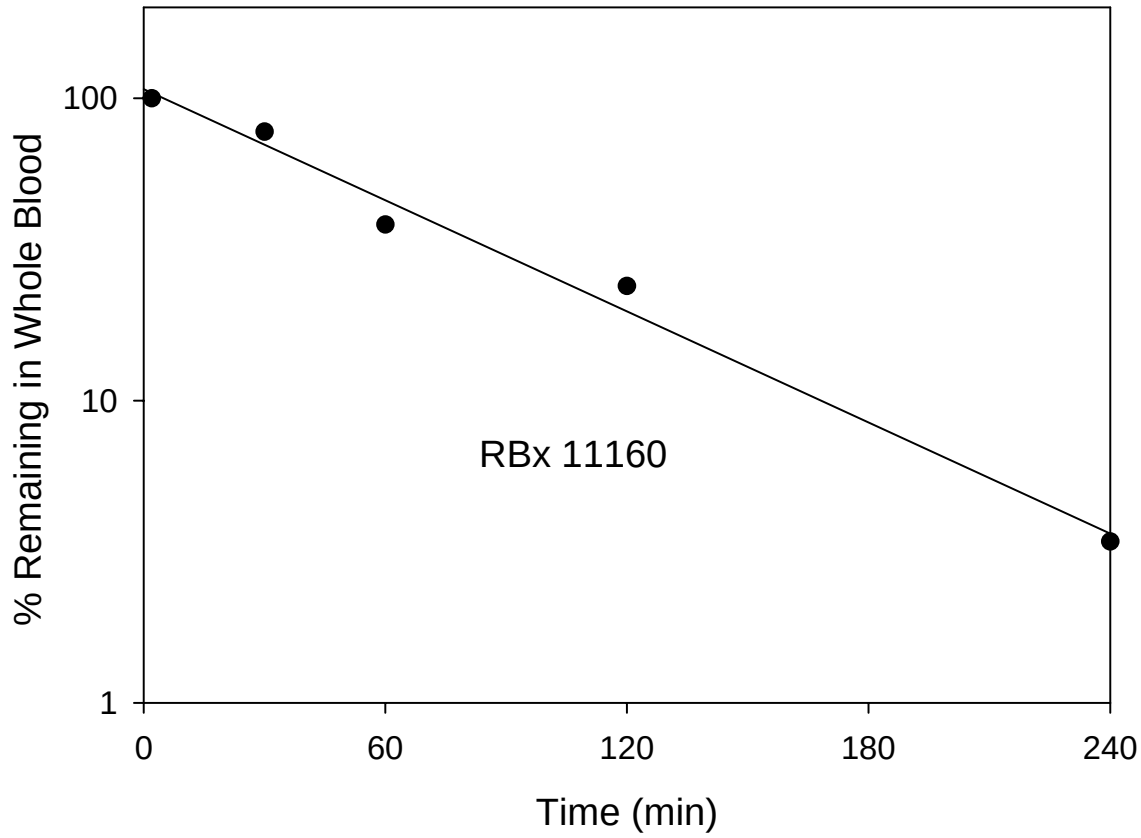
OZ Clearance in Red Blood Cells

- First Generation OZ exhibited relatively rapid degradation in whole blood *in vitro*



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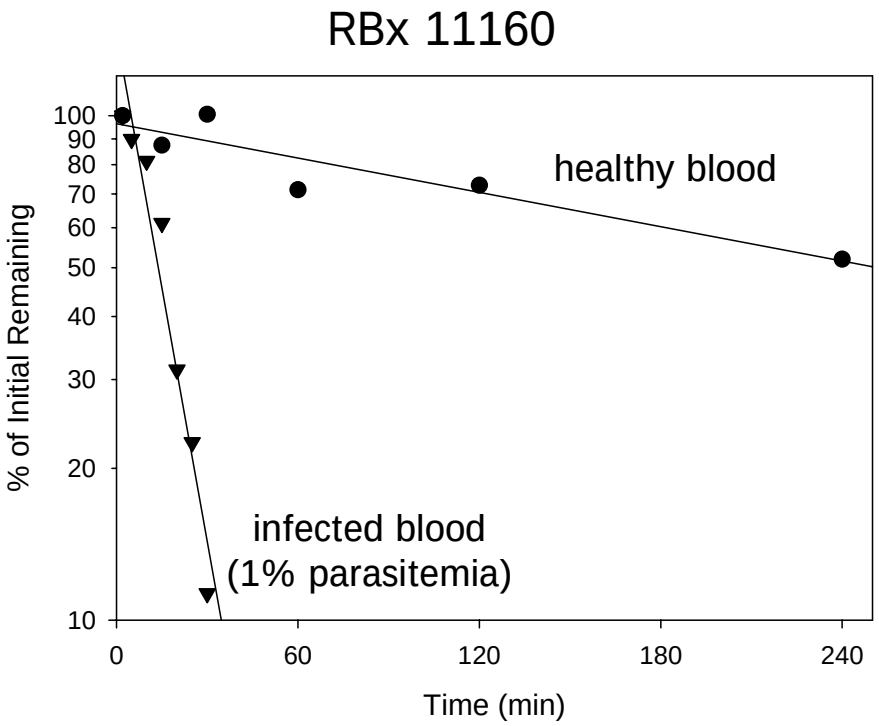
In Vitro Degradation in Infected Blood

- Rapid *in vitro* degradation of RBx 11160 in **infected blood**



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Second Generation of Synthetic Peroxides

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OZ Clearance in Red Blood Cells

- Fe(II)-mediated cleavage likely to be a significant contributor to the *in vivo* clearance of RBx 11160
- Can we modify the OZ structure to reduce the rate of cleavage without compromising biological activity?
- The answer is...Yes

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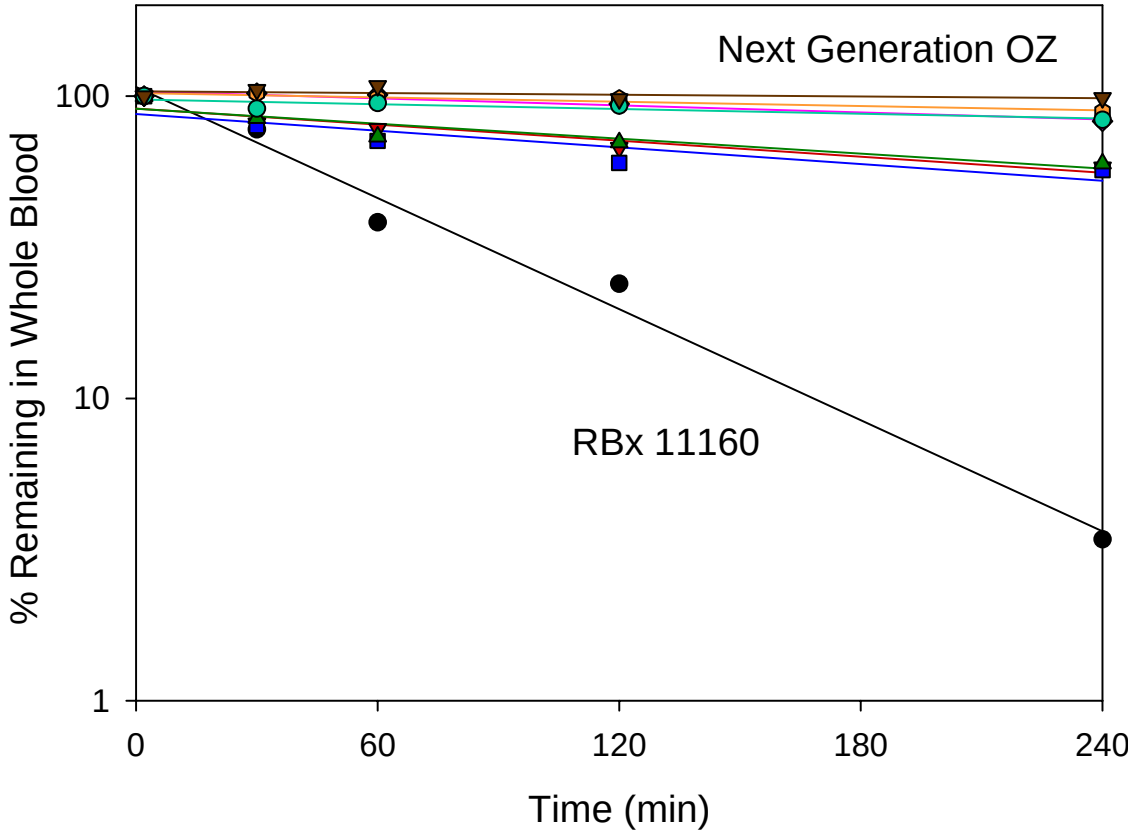
OZ Clearance in Red Blood Cells

- Next Generation OZ are significantly more stable in whole blood *in vitro* than First Generation OZ



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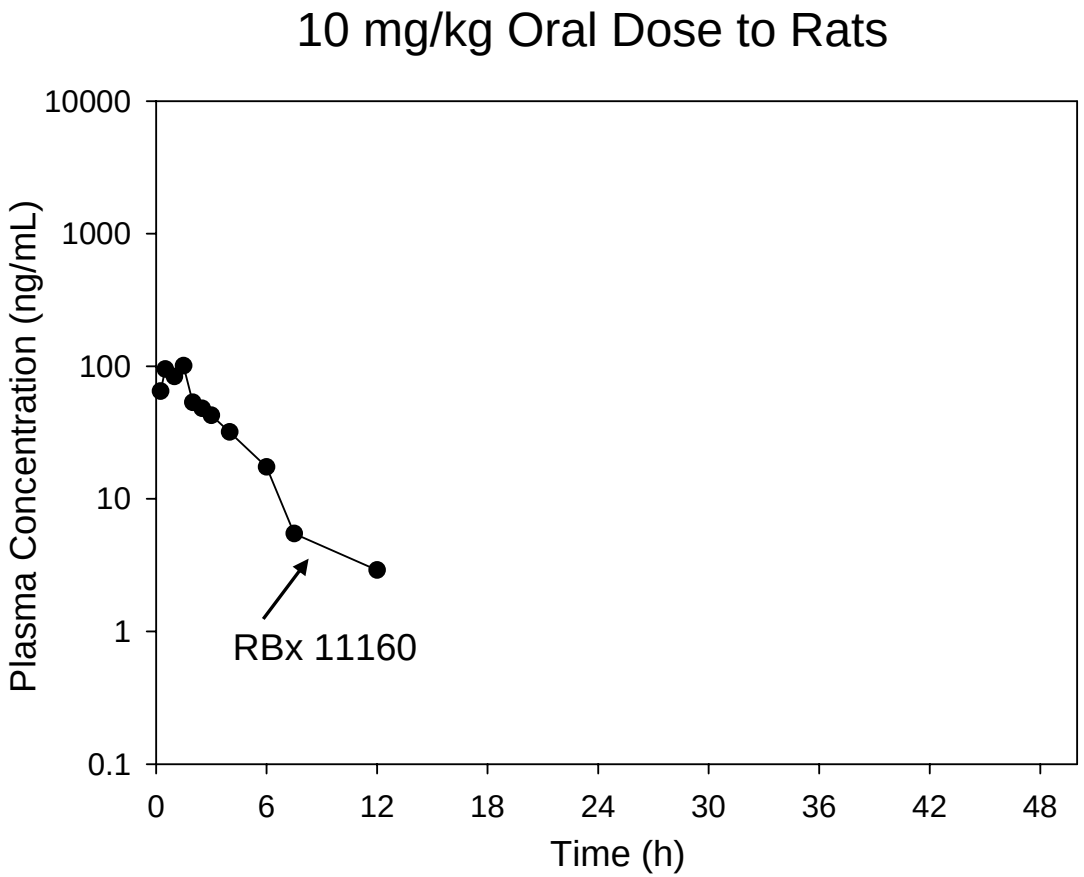
Increased Stability of Next Generation OZs

- Greater stability in blood contributes to better exposure, longer half-life ...and biological activity is better!



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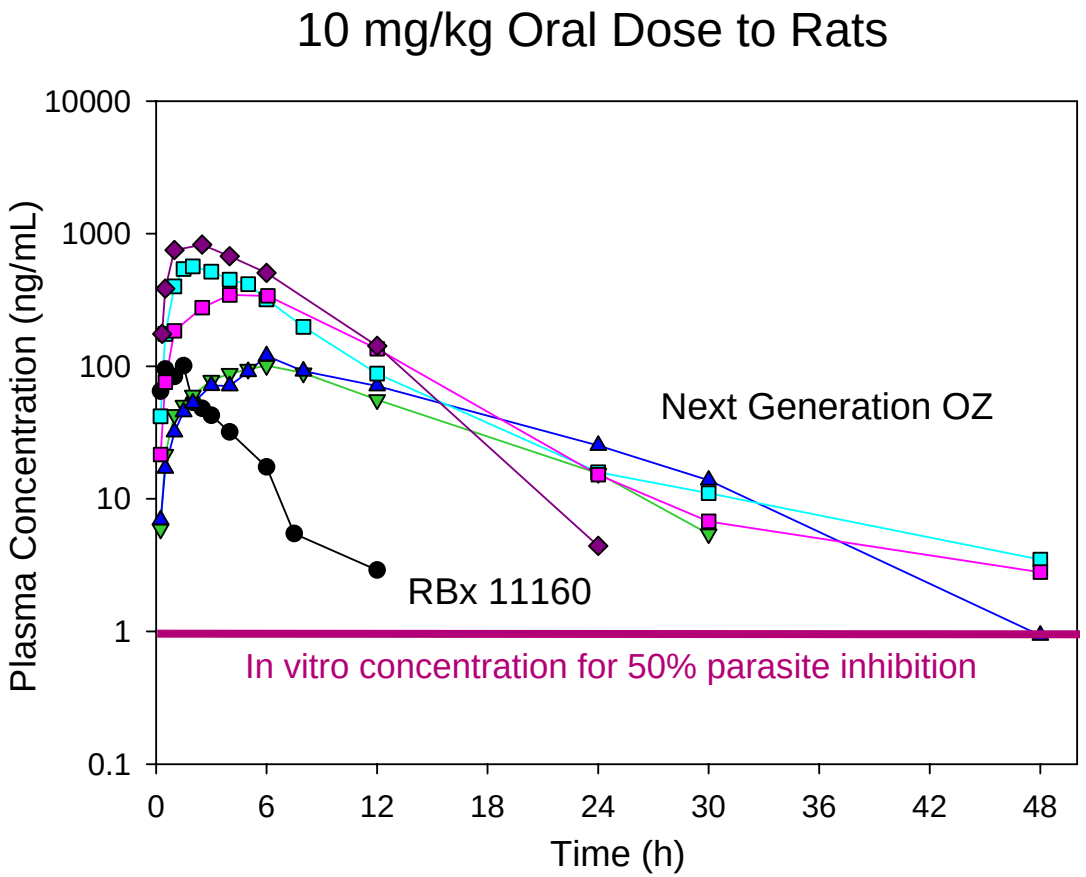

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Antimalarial Activity in Mice

Single 30 mg/kg oral dose to mice (*P. berghei*)

Compound (mg/kg)	Survival (d), Cure (%)
Artesunate	9 d, 0%
Artemether	9 d, 0%
Chloroquine	10 d, 0%
Mefloquine	22 d, 0%
RBx 11160	11 d, 0%
No treatment	6 d, 0%

Limited survival; no cures with artemisinin derivatives, conventional drugs or RBx 11160

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Compound (mg/kg)	Survival (d), Cure (%)	Compound (mg/kg)	Survival (d), Cure (%)
Artesunate	9 d, 0%	OZ401	25 d, 64%
Artemether	9 d, 0%	OZ439	>30 d, 100%
Chloroquine	10 d, 0%	OZ460	25 d, 60%
Mefloquine	22 d, 0%	OZ461	>30 d, 100%
RBx 11160	11 d, 0%	OZ464	>30 d, 100%
No treatment	6 d, 0%	OZ466	>30 d, 100%
		OZ482	>30 d, 100%
		OZ485	25 d, 40%
		OZ493	>30 d, 100%

Survival and 100% cure for Next Generation OZ

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Prophylaxis in Mice

30 mg/kg given 24 h prior to *P. berghei* infection (mice)

Compound (mg/kg)	Survival (d), Prophylaxis (%)
Artesunate	7 d, 0%
Artemether	n.t.
Chloroquine	7 d, 0%
Mefloquine	27 d, 60%
RBx 11160	7 d, 0%
No treatment	6 d, 0%

Only mefloquine has prophylactic properties

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		OZ482	24 d, 60%
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		OZ493	24 d, 60%

Three next generation OZ are 100% prophylactic and are superior to mefloquine

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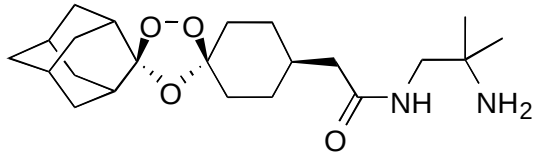
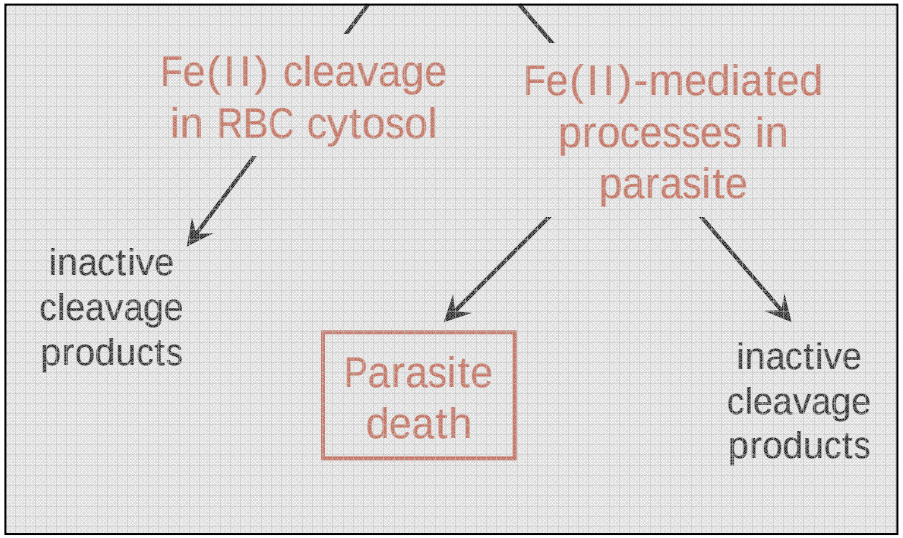
OZ Cleavage Accelerated in Infected Blood



RBx 11160

Infected RBC



competing processes in infected RBCs are not well defined

- High concentrations of Fe(II) haem in the parasite
- Rapid cleavage of RBx11160 in the presence of parasites

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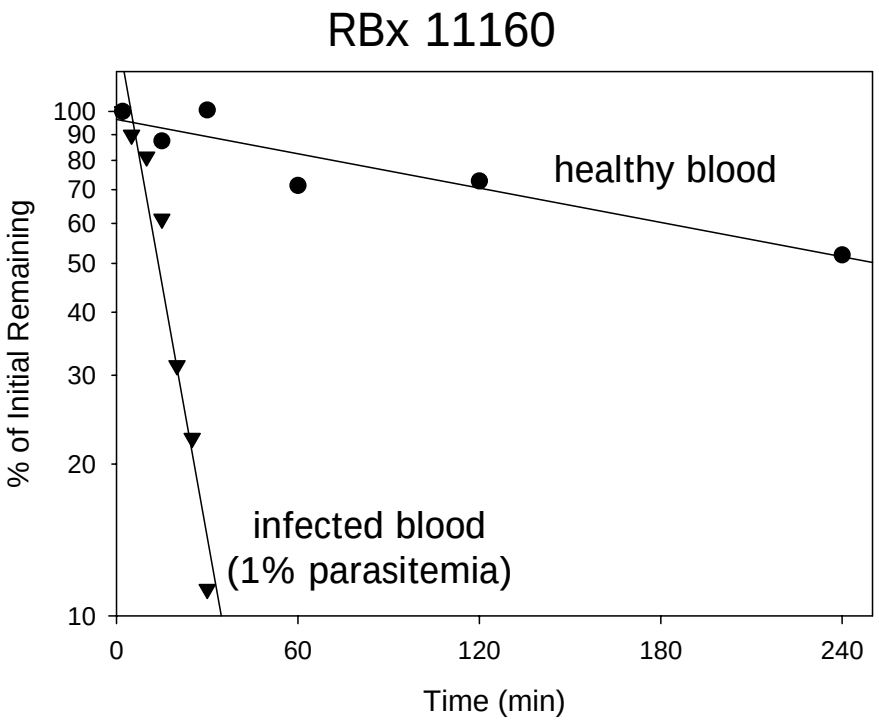
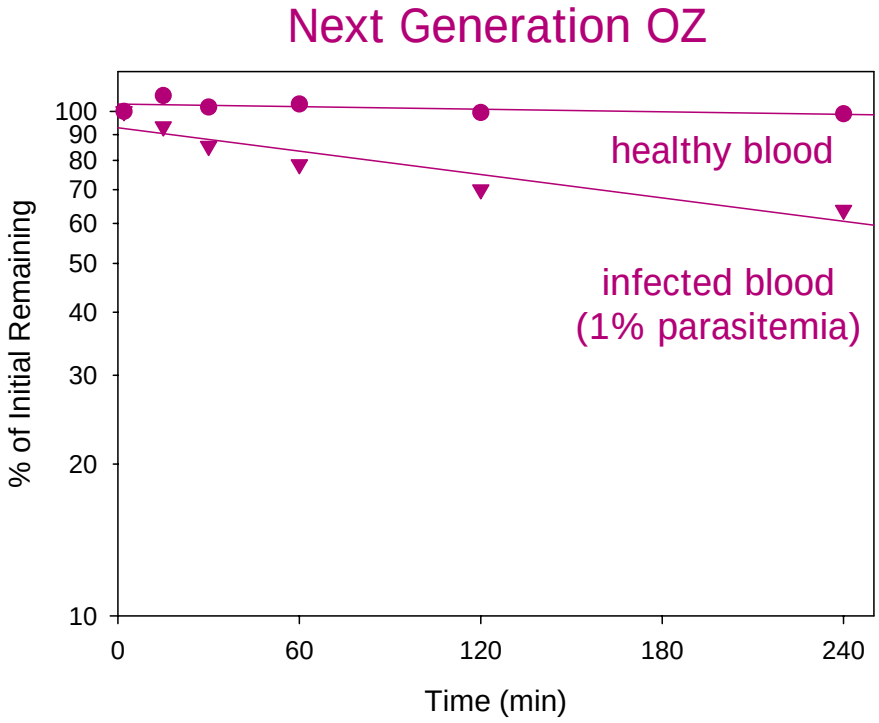
In Vitro Degradation in Infected Blood

- Next Generation OZ significantly more stable in healthy and especially infected blood





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Conclusions

- Fe(II)-mediated cleavage in RBCs contributes to the *in vivo* clearance of RBx 11160 (and possibly other peroxides)
- Structural modifications for Next Generation OZ have resulted in:
  - improved stability in blood
  - reduced *in vivo* clearance, prolongation in half-life and increased exposure in rats
  - enhanced biological activity in well-established mouse model of malaria
  - excellent prophylactic activity in mice – exceeds that of the benchmark chemoprophylactic, mefloquine (Lariam®)

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Timelines

Microsoft Project - Synthetic peroxide to launch.mpp

File Edit View Insert Format Tools Project Collaborate Window Help

	Task Name	Finish
1	Lead Optimization	Wed 31.10.07
2	**Candidate Selection**	Wed 31.10.07
3	Regulatory Toxicity Studies	Tue 30.12.08
4	**Decision FTIH**	Tue 30.12.08
5	Phase I	Tue 16.06.09
6	Phase II PoC	Tue 23.02.10
7	phase I combination	Tue 01.12.09
8	phase II DRF monotherapy	Tue 02.11.10
9	phase II combination	Tue 12.07.11
10	**APAC**	**Tue 12.07.11**
11	Pivotal phase III A	Tue 20.03.12
12	Pivotal phase III B	Tue 20.03.12
13	Preparation of reg filing	Tue 04.09.12
14	**Submission of filing**	Tue 04.09.12
15	Regulatory approval process	Tue 14.05.13
16	**Launch**	Tue 14.05.13

2-MMV Tracking View

2008 2009 2010 2011 2012 2013 2014

Lead Optimization
Regulatory Toxicity Studies
Phase I
Phase II PoC
phase I combination
phase II DRF monotherapy
phase II combination
Pivotal phase III A
Pivotal phase III B
Preparation of reg filing
Regulatory approval process

Launch > Q3 2013

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Partners

- Medicinal and synthetic chemistry

  University of Nebraska

- *In vitro* activity and *in vivo* efficacy assessment

  Swiss Tropical Institute, Basel

- ADME, lead optimisation and compound profiling

  Monash University

- Project managment and funding

  MMV

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