

Malaria

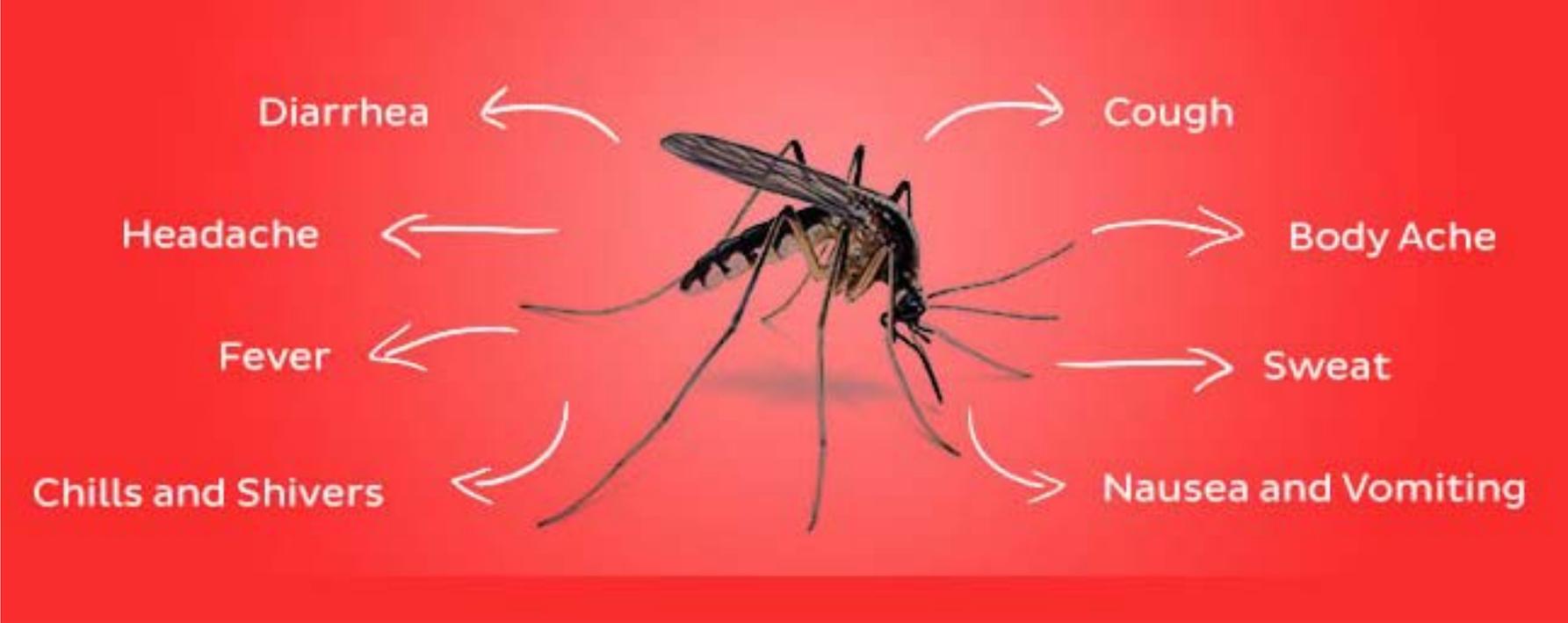


Malaria: vektoren

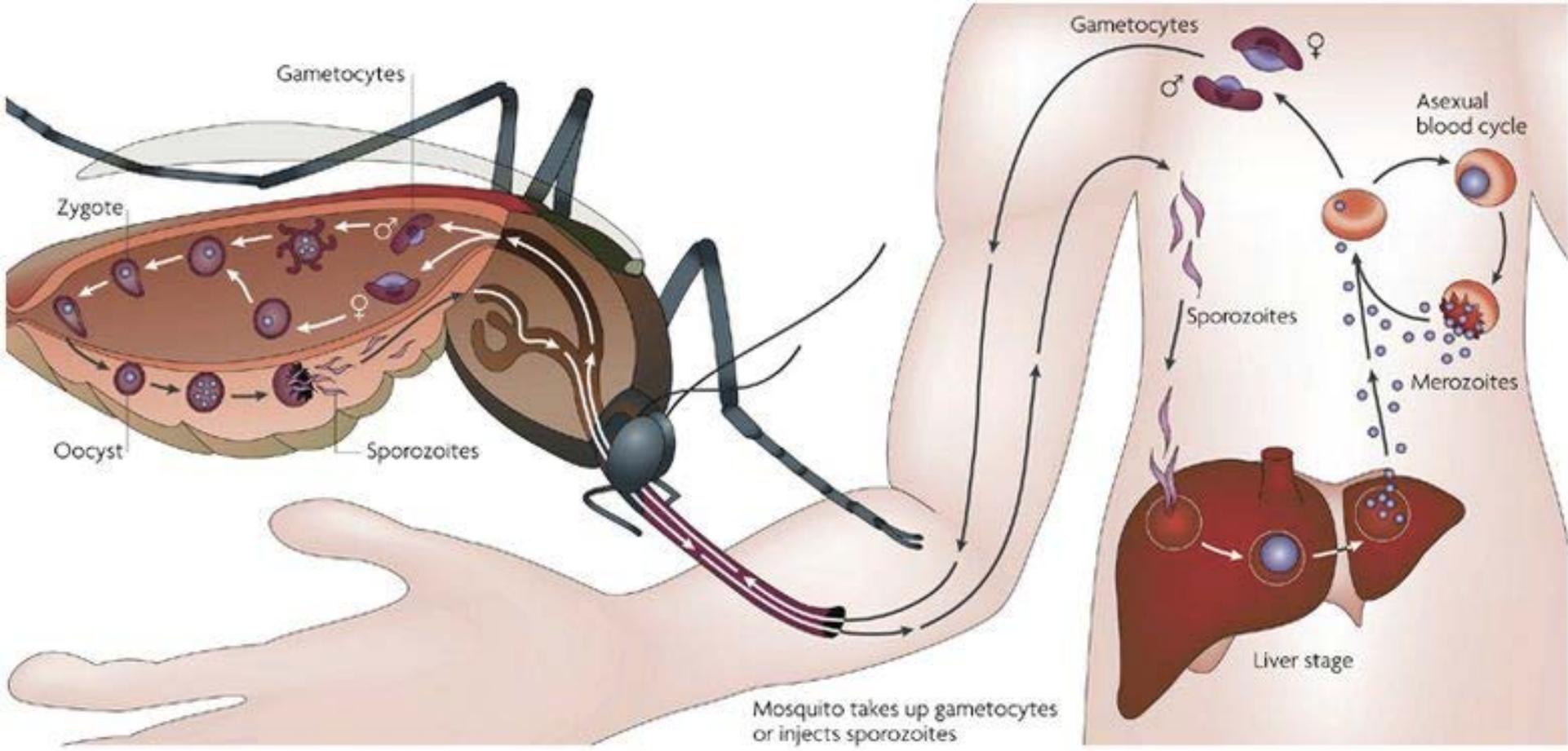


Anopheles

Malaria: symptomer



Malaria: *Plasmodium falciparum* cyklus



Mosquito takes up gametocytes or injects sporozoites

Malaria: forbedringer i smitte og dødelighed

www.who.int/malaria/en/

for WHO updates

PAHO



Cases

214 million

malaria cases estimated worldwide in 2015

Incidence

37%

global decrease in malaria incidence between 2000 and 2015

Mortality

60%

decrease in global malaria mortality rates between 2000 and 2015

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2017: 219 million cases (2015–2017 no significant progress), 435 000 deaths (2010: 607 000)

Africa 200 million (92%)

Nigeria (25%) - Democratic Republic of the Congo (11%) - Mozambique (5%) - India (4%) - Uganda (4%)

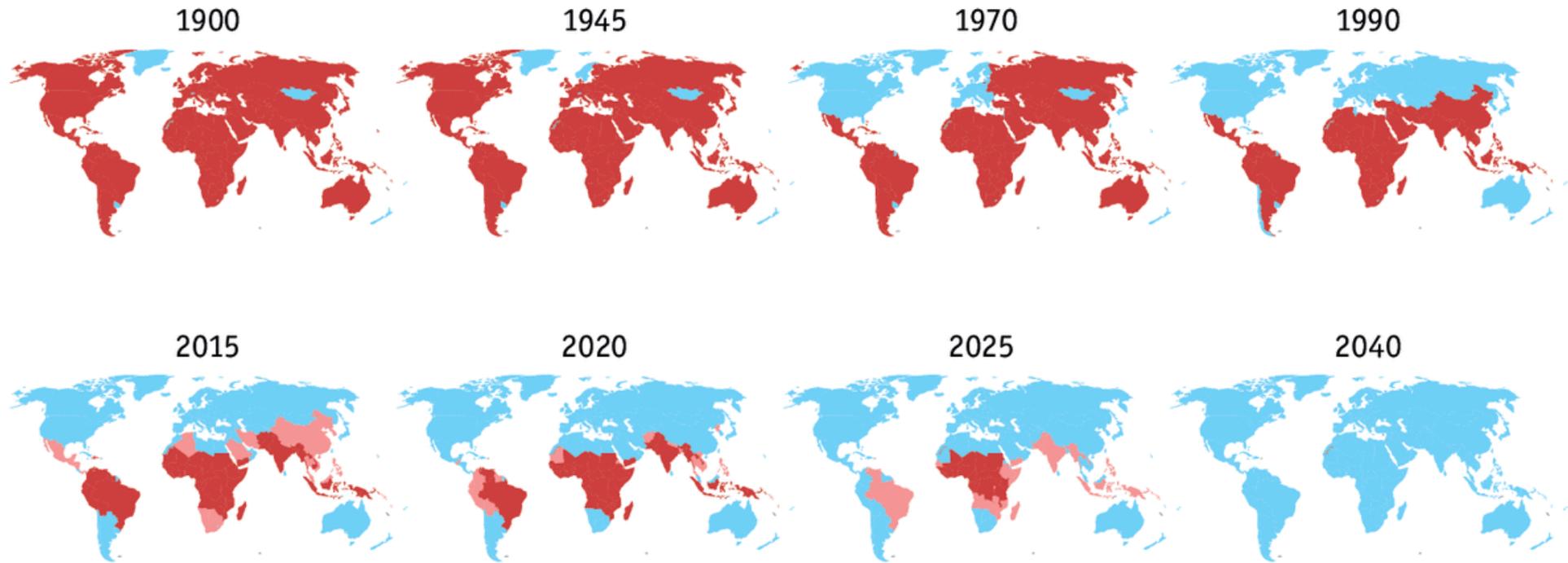
South-East Asia incidence rate fall – 2010: 17 per 1000, 2017: 7 per 1000

Parasite:

Plasmodium falciparum: Africa 99.7% of cases, South-East Asia 62.8%

Plasmodium vivax: Americas 74.1%

Malaria: udbredelsen svinder ind



MALARIA

An infectious disease characterized by cycles of chills, fever, and sweating, caused by a protozoan of the genus *Plasmodium* in red blood cells, which is transmitted to humans by the bite of an infected female anopheles mosquito.

247 MILLION APPROX. CASES OF MALARIA EACH YEAR

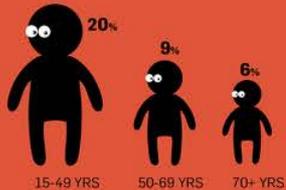
3.3 BILLION PEOPLE LIVE IN AREAS WHERE MALARIA IS A CONSTANT THREAT



700,000 malaria deaths among African children under age 5, or about 56% of all global malaria deaths

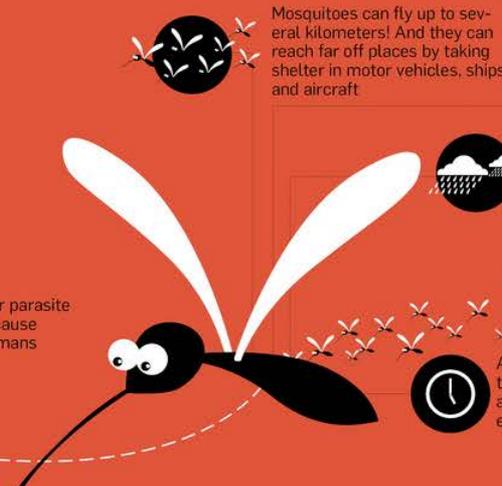
1.2 MILLION DEATHS IN 2010

95% DEATH IS IN AFRICA



MALARIA DEATHS IN ADULTS

4 There are four parasite species that cause malaria in humans



Mosquitoes can fly up to several kilometers! And they can reach far off places by taking shelter in motor vehicles, ships and aircraft



The female mosquito lays 30-150 eggs every 2-3 days. Human blood is needed to nourish these eggs.



Anopheles mosquitoes breed in natural water collections. Therefore, breeding increases dramatically in the rainy season



Anopheles mosquitoes enter the house between 5 p.m. and 9.30 p.m. and again in early hours of morning



\$1.2 BILLION WAS SPENT BY THE GATES FOUNDATION FROM 2000-'08, FOR MALARIA ERADICATION

\$100 MILLION A YEAR IS NEEDED FOR MALARIA RESEARCH

25% COMING FROM THE UNITED STATES

SYMPTOMS OF MALARIA

- CENTRAL**
 - HEADACHE
- SYSTEMIC**
 - FEVER
- MASCULAR**
 - FATIGUE
 - PAIN
- BACK**
 - PAIN
- SKIN**
 - CHILLS
 - SWEATING
- RESPIRATORY**
 - DRY COUGH
- SPLEEN**
 - ENLARGEMENT
- STOMACH**
 - NAUSEA
 - VOMITING

7-21

The time between a mosquito bite and the start of illness is usually

2 Sporozoites travel through the bloodstream to the liver, mature, and eventually infect the human red blood cells

3 When an Anopheles mosquito bites a human, these sporozoites complete and repeat the complex *Plasmodium* life cycle



60% of outpatient health clinic visits.

40% up to 40% of public health expenditures;

30-40% of inpatient hospital admissions

Economic and health system impact on heavily affected country



Quinine is purified and used to treat malaria

Anti-malaria drug Chloroquine is discovered

A parasite is successfully grown in culture and vaccine research is possible

Anti malaria drug Mefloquine Hydrochloride is approved

Malaria vaccine candidate RTS,S is developed and enters clinical trials

Mosquito nets, now commonly known as insecticide-treated mosquito nets (ITNs) are shown to reduce overall childhood mortality by 20%

The final stage of clinical trials of Mosquirix find it halves the risk of african children getting malaria

The vaccine is set to be licenced and hit the market

25%

The Malaria mortality rates that has fallen globally since 2000

Source: Various. This graphics is not meant for any commercial purposes. Graphics.RAJ

Q&A on artemisinin resistance

July 2016

WHO
anbefaler

1. What is artemisinin?

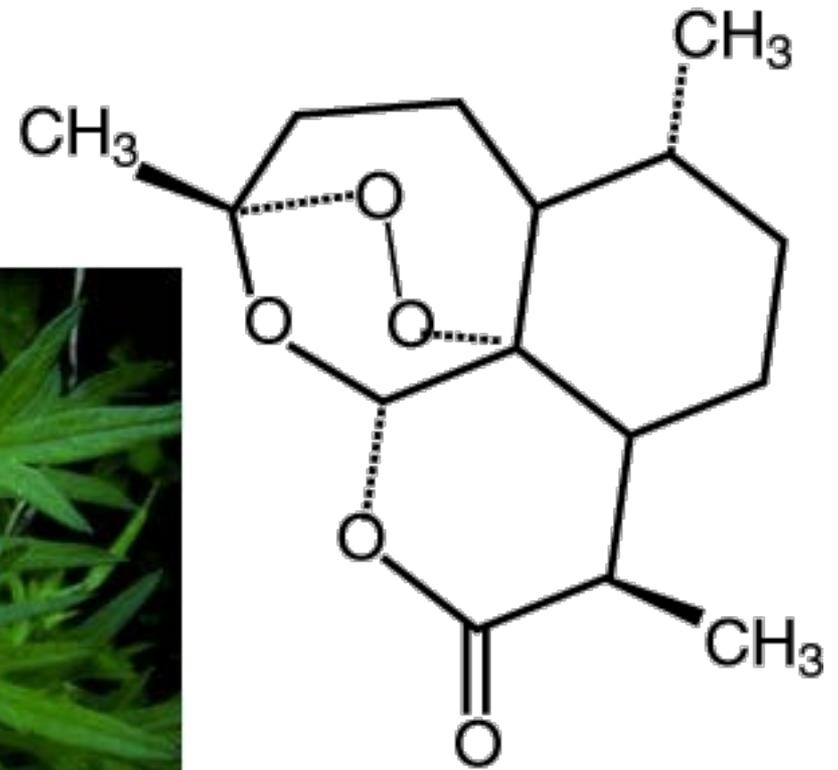
Isolated from the plant *Artemisia annua*, or sweet wormwood, artemisinin and its derivatives are powerful medicines known for their ability to swiftly reduce the number of *Plasmodium* parasites in the blood of patients with malaria. Artemisinin-based combination therapies (ACTs) are recommended by WHO as the first-line treatment for uncomplicated *P. falciparum* malaria. Expanding access to ACTs in malaria-endemic countries has been integral to the remarkable recent success in reducing the global malaria burden. The number of ACT treatment courses procured from manufacturers increased globally from 11 million in 2005 to 337 million in 2014.

ACTs combine artemisinin derivatives with a partner drug. The role of the artemisinin compound is to reduce the main parasite load during the first 3 days of treatment, while the role of the partner drug is to eliminate the remaining parasites. In patients who are infected with artemisinin-resistant strains of malaria, the artemisinin compound does not clear all parasites by the third day of treatment. However, patients are still cured as part of a longer treatment regimen, provided that they are treated with an ACT containing a partner drug that is effective in that geographical area. WHO currently recommends 5 different ACTs.

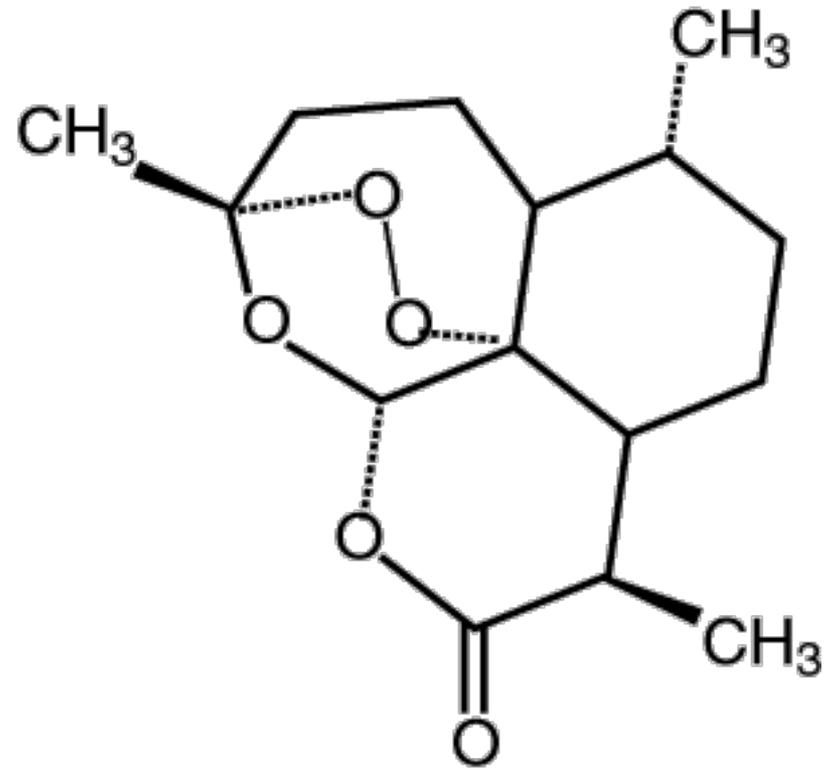
2. What is the state of artemisinin resistance around the world?

As of July 2016, artemisinin resistance has been confirmed in 5 countries of the Greater Mekong subregion (GMS): Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. In the large majority of sites, patients with artemisinin-resistant parasites still recover after treatment, provided that they are treated with an ACT containing an effective partner drug. However, along the Cambodia-Thailand border, *P. falciparum* has become resistant to almost all available antimalarial medicines. There is a real risk that multidrug resistance will soon emerge in other parts of the subregion as well.

Artemisinin: oprindeligt fundet i planteekstrakt



Artemisinin: Tu Youyou



1960'erne og 70'erne:

- screener over 2000 traditionelle kinesiske opskrifter
- genopdager metode i 'Håndbog for recepter til akut behandling' fra 340 af Ge Hong
- tester udtræk af *Artemisia annua* på mus og aber
- tester udtræk på sig selv

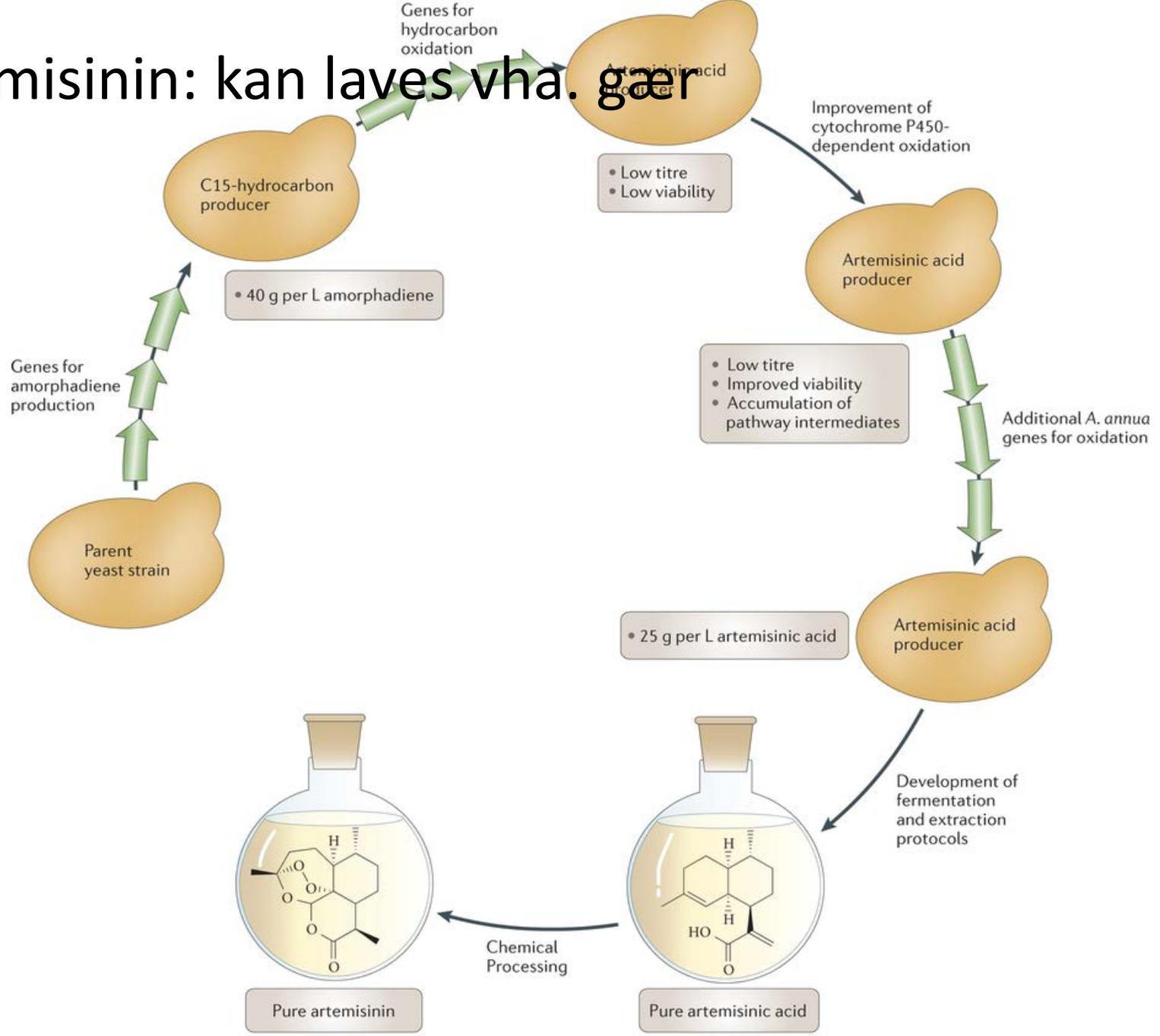
2015:

Nobelpris i medicin og fysiologi

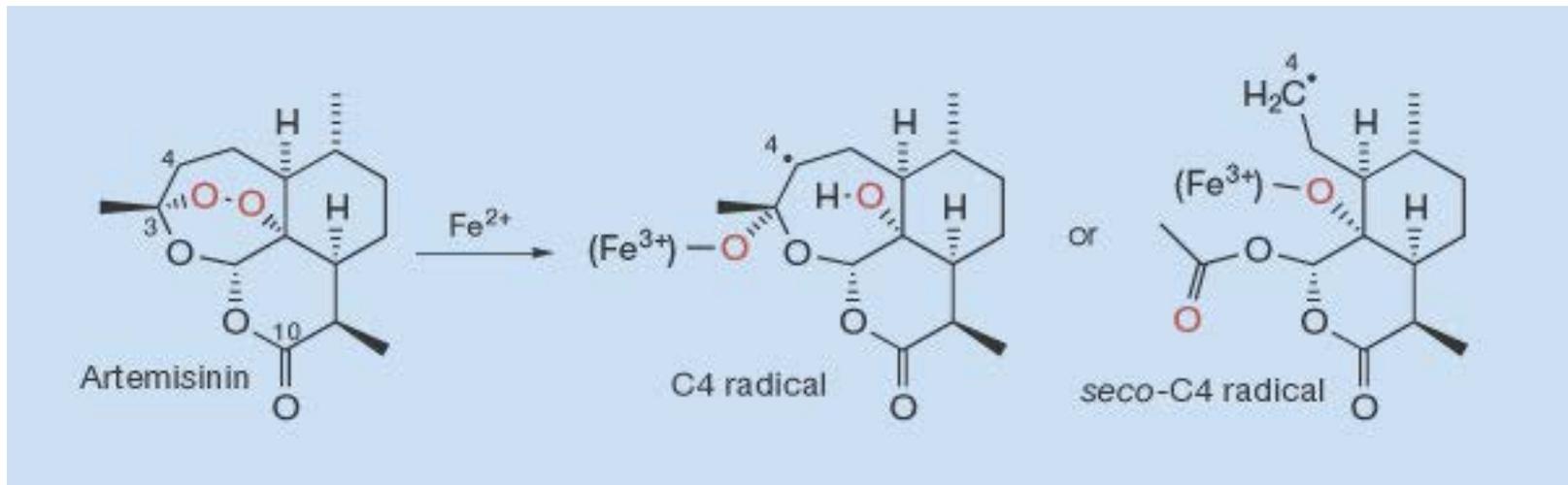
Artemisinin: kan laves vha. gær



Artemisinin: kan laves vha. gær



Artemisinin: reagerer med jern i røde blodlegemer og danner frit radikal



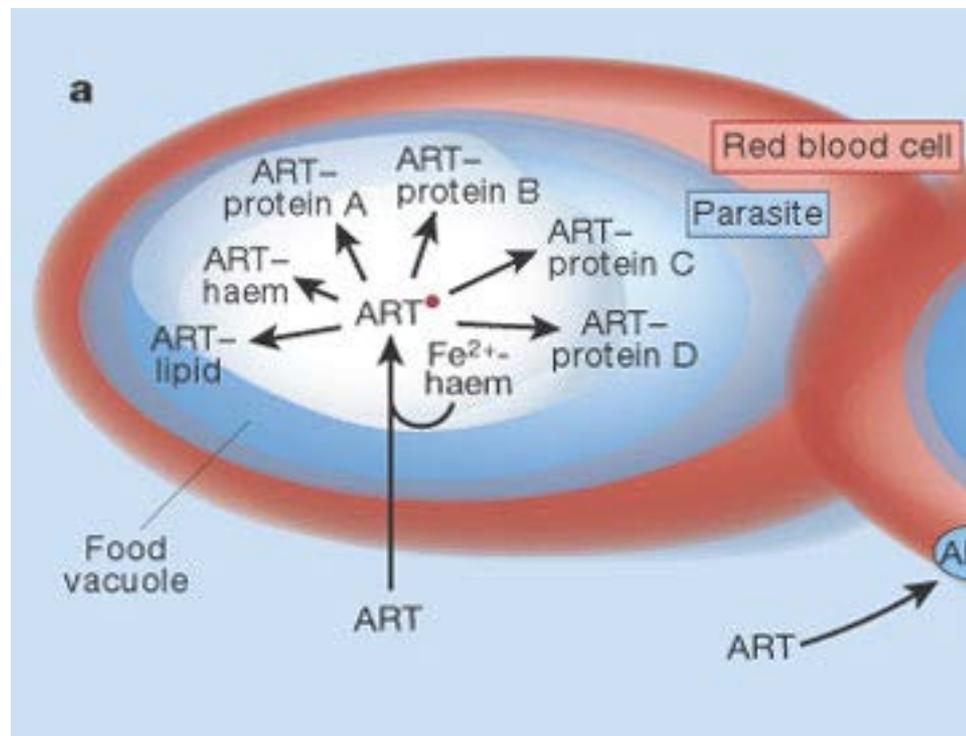
Peroxidbro (rød) kløves ved interaktion med Fe^{2+}

'C4' og 'seco-C4' frie radikaler kan modificere biomolekyler

Artemisinin: hvilke molekyler påvirker det?

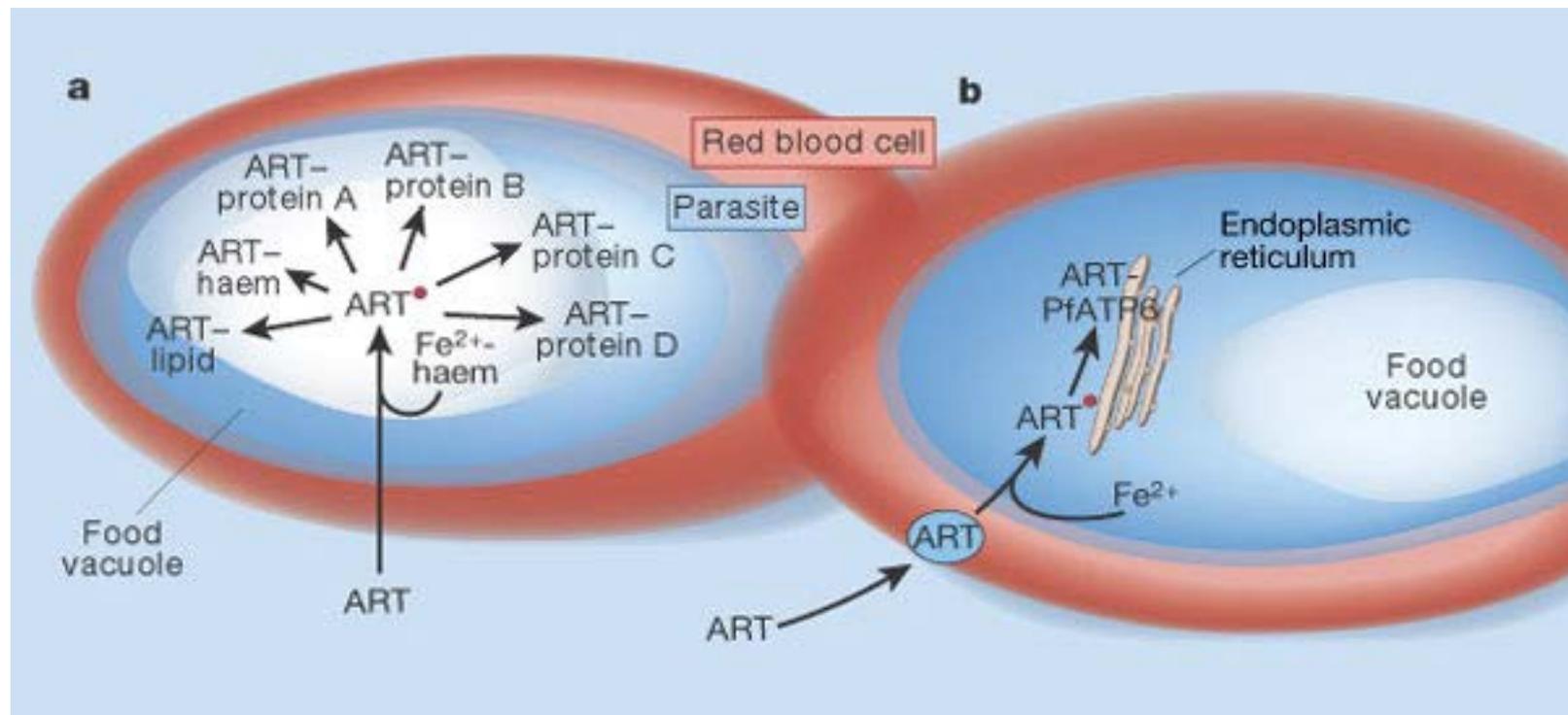


Artemisinin: hvilke molekyler påvirker det?





Artemisinin: hvilke molekyler påvirker det?



Artemisinin: hvilke molekyler påvirker det?

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News and Views

Nature 424, 887-889 (21 August 2003) | doi:10.1038/424887a

Malaria: To kill a parasite

Robert G. Ridley¹

Artemisinins have been used since ancient times to treat malaria. A new theory could explain how this age-old medicine is able to cause the death of the malaria parasite. ▲ Top

The Chinese herb qinghao (*Artemisia annua*) has long been used to treat malaria — Taoist manuscripts dating back to the third century describe the use of qinghao extracts to treat malaria-related fevers¹. Over the past two decades, derivatives of the herb's active ingredient, artemisinin, have made an increasing contribution to malaria treatment. But the precise mechanism by which artemisinin derivatives kill the parasite has remained obscure. Writing on [page 957](#) of this issue, Krishna and colleagues² propose a radical new theory to explain the molecular basis of the antimalarial activity of artemisinin.

Malaria remains a scourge of the developing world, killing over a million people each year and infecting around 500 million³. Most of the victims are children

Artemisinin: hvilke molekyler påvirker det?

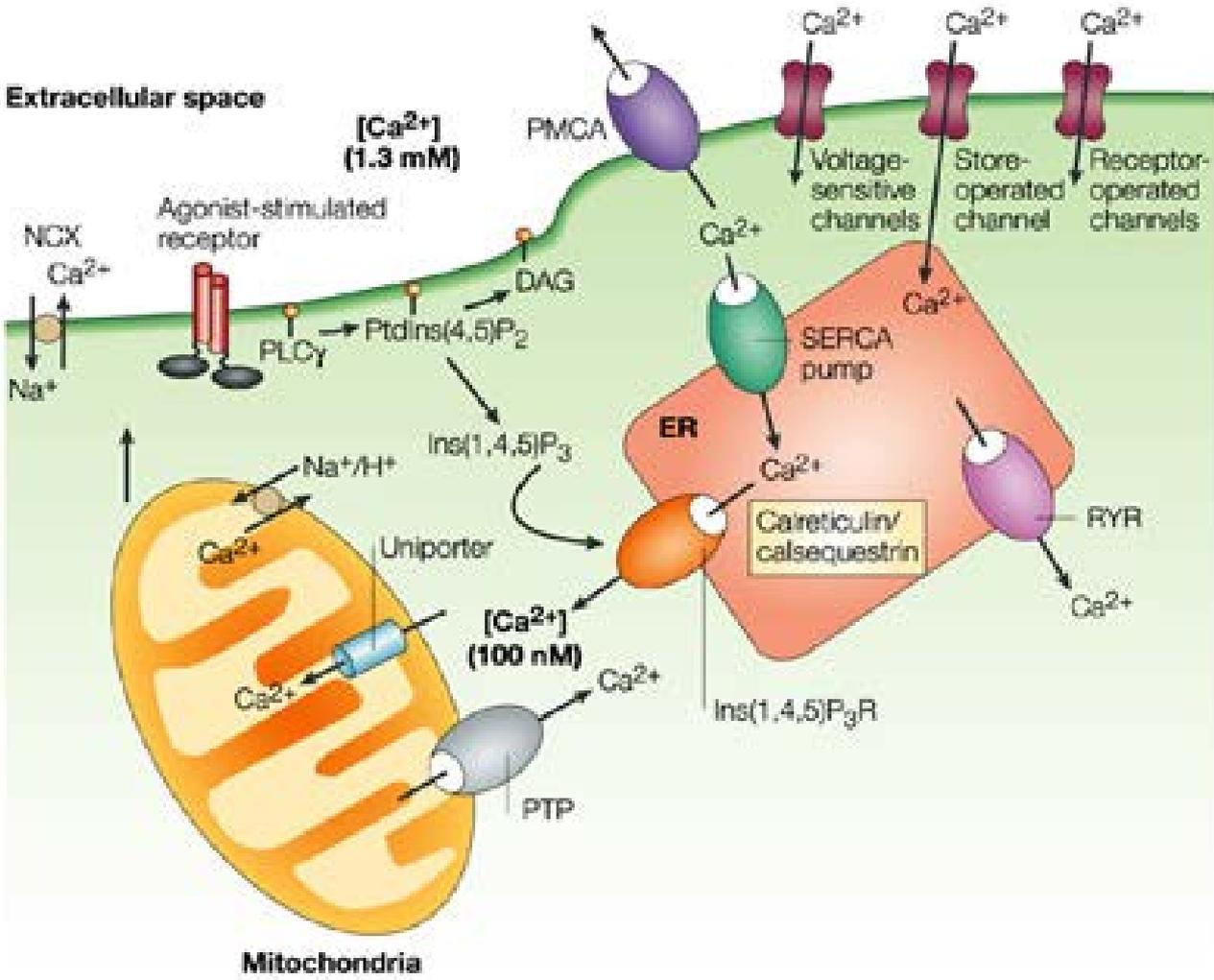
Artemisinins target the SERCA of *Plasmodium falciparum*

U. Eckstein-Ludwig¹, R. J. Webb¹, I. D. A. van Goethem², J. M. East², A. G. Lee², M. Kimura³, P. M. O'Neill⁴, P. G. Bray⁵, S. A. Ward⁵ & S. Krishna¹

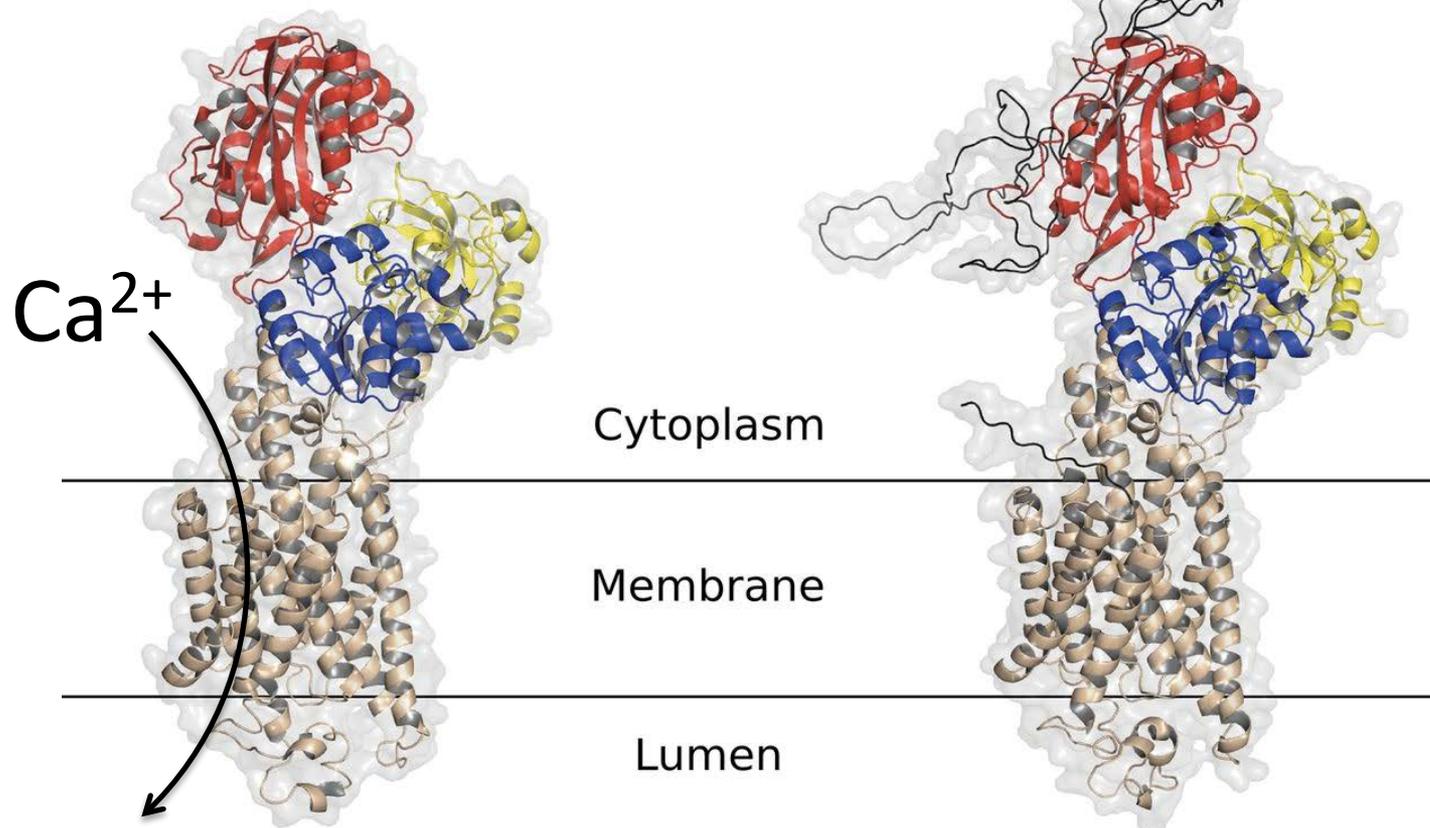
1. Department of Cellular and Molecular Medicine, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK

Nature 2003

SERCA: en calciumpumpe (sarco-endo-plasmatic reticulum)



SERCA: en calciumpumpe



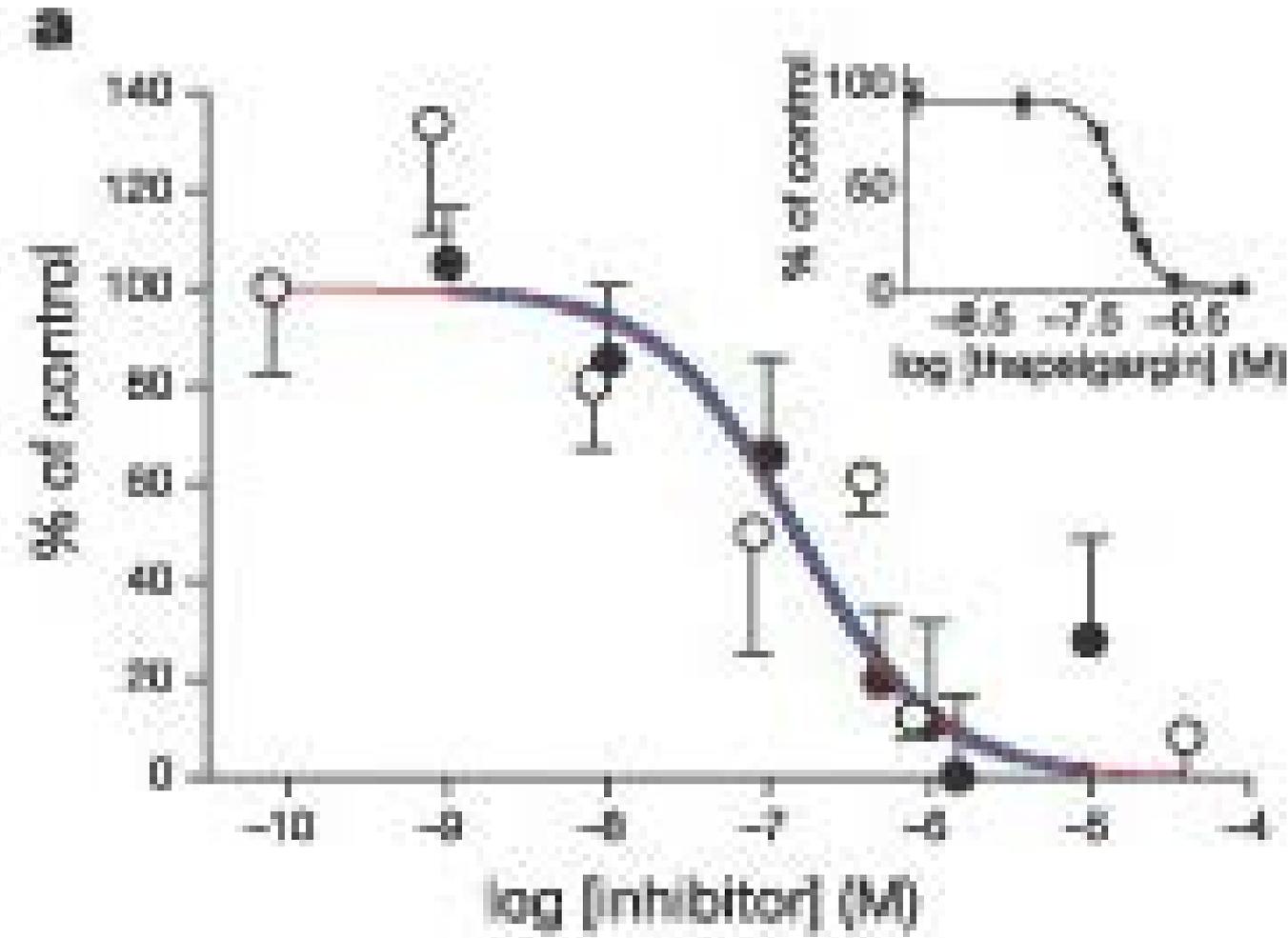
SERCA1a

**PfATP6
(model)**

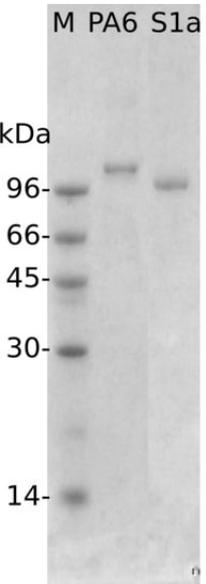
A

B

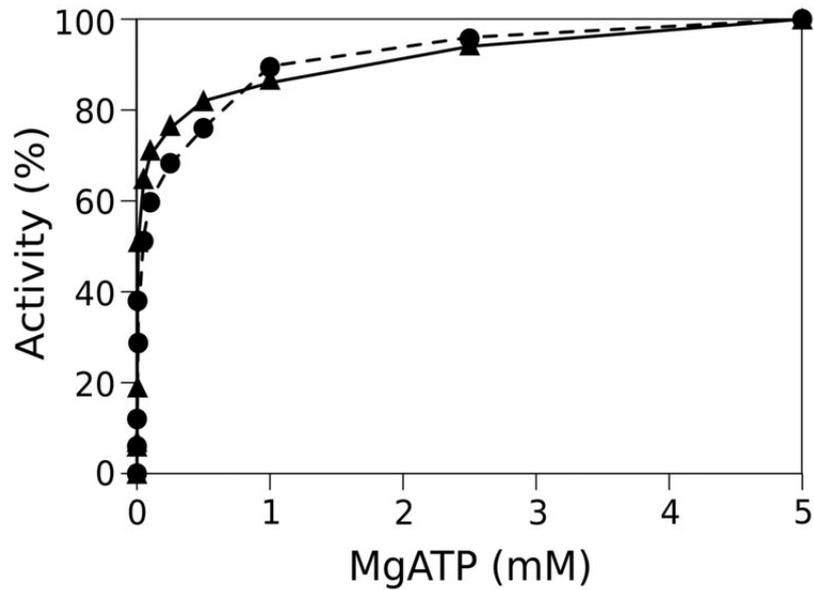
Artemisinin: inhibitor of parasite calcium pump



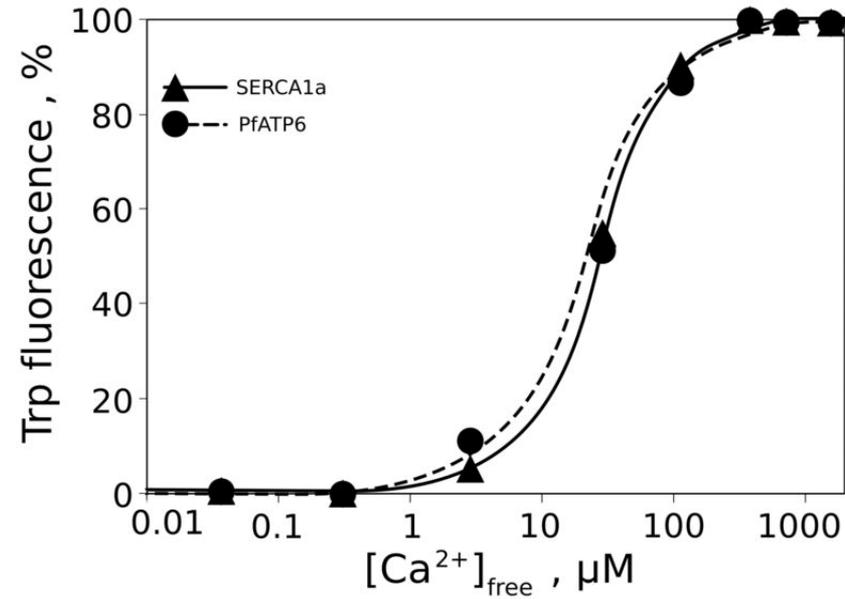
Artemisinin: inhiberer parasittens calciumpumpe ..eller gør det?



A

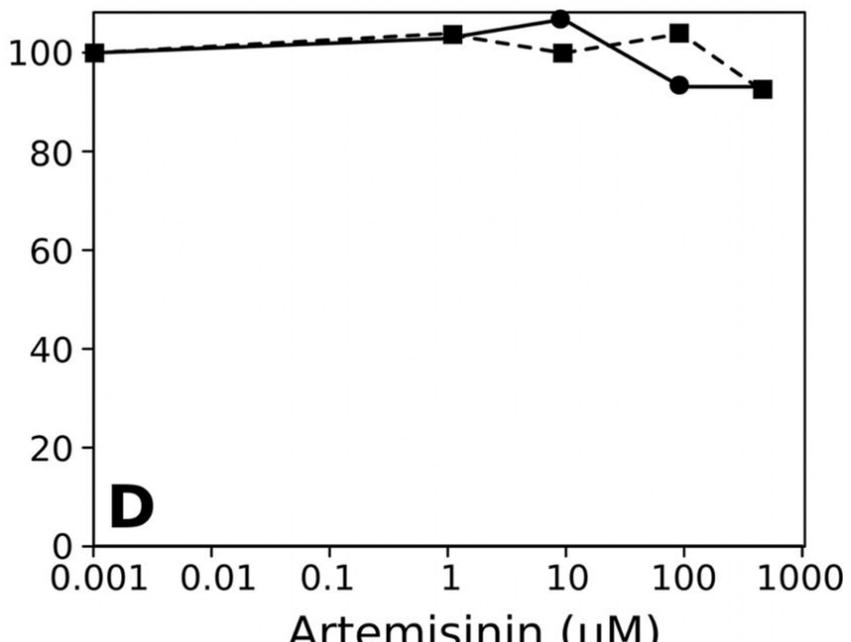
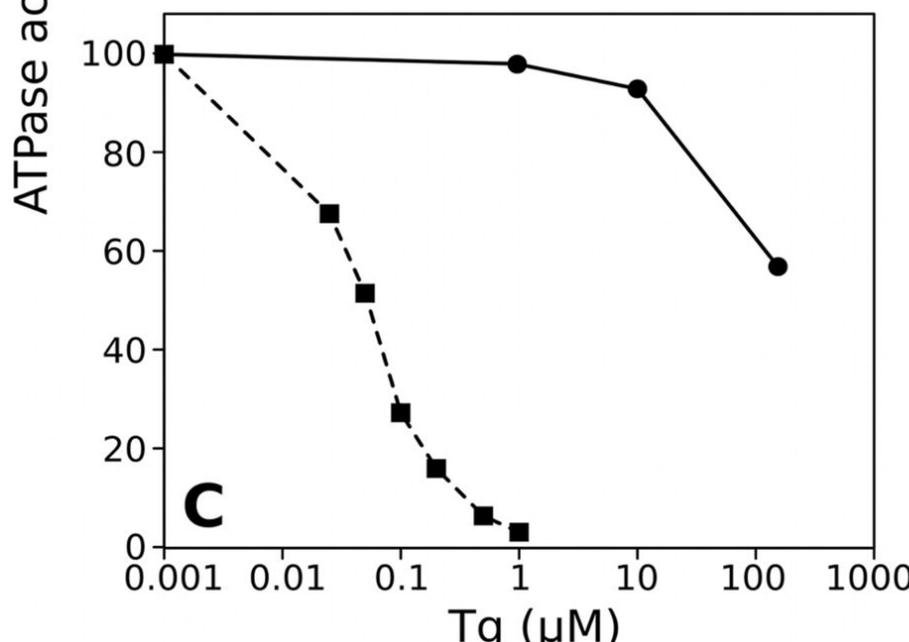
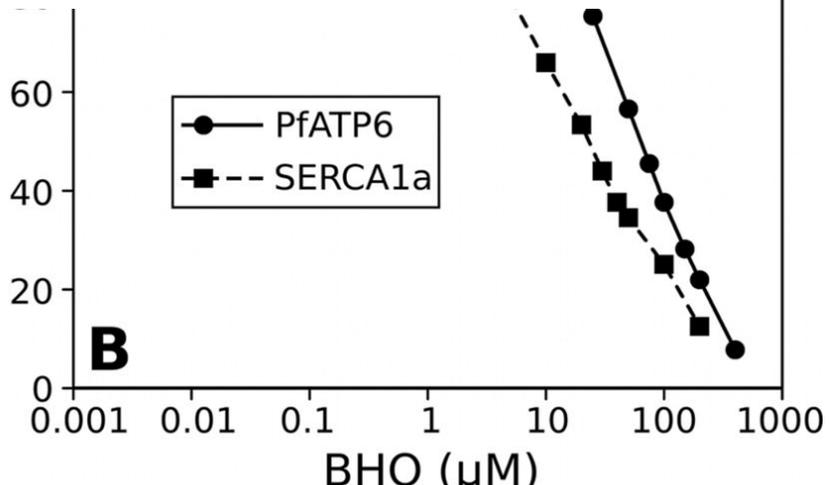
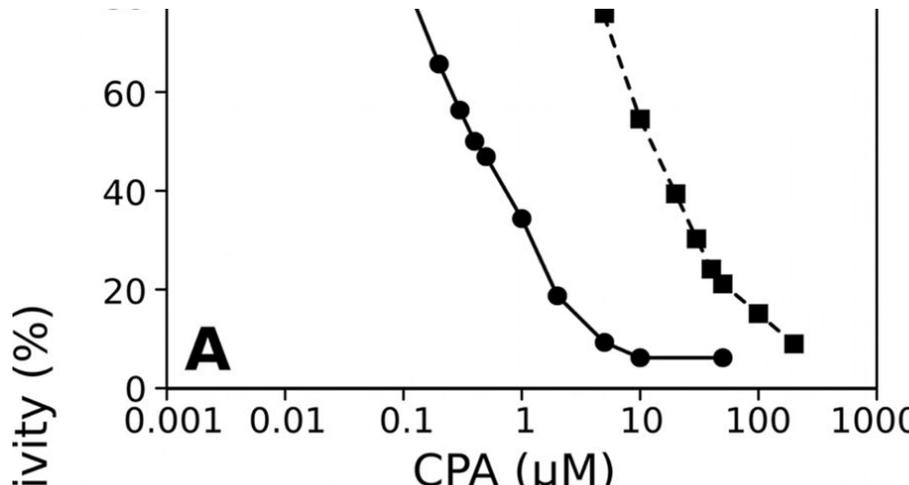


B



C

Artemisinin: inhiberer parasittens calciumpumpe ..eller gør det?



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NATURE STRUCTURAL & MOLECULAR BIOLOGY | CORRIGENDUM



A single amino acid residue can determine the sensitivity of SERCAs to artemisinins

Anne-Catrin Uhlemann, Angus Cameron, Ursula Eckstein-Ludwig, Jorge Fischbarg, Pavel Iserovich, Felipe A Zuniga, Malcolm East, Anthony Lee, Leo Brady, Richard K Haynes & Sanjeev Krishna

Nature Structural & Molecular Biology **19**, 264 (2012) | doi:10.1038/nsmb0212-264



PDF



Citation



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Article metrics

Nat. Struct. Mol. Biol. **12**, 628–629 (2005); published online 5 June 2005; corrected after print 3 February 2012

Note: U.E.-L. was unavailable to comment on this corrigendum.

**a****M3**

<i>P. falciparum</i>	256	PLQIKIDLFGQQLSKIIFVICVTVWII
<i>P. vivax</i>	256	PLQIKIDAFGRQLSKIIFVICVTVWVI
<i>P. yoelii</i>	256	PLQIKIDSFGKQLSKIIFVICVTVWII
<i>P. berghei</i>	256	PLQIKIDSFGKQLSKIIFVICVTVWII
SERCA1	248	PLQQLLDEFGEQLSKVISLIVAVWLI

M5

<i>P. falciparum</i>	952	FNTIVEAIKEGRCIYNNMKAFIRYLISSNIGEVASIFITALE
<i>P. vivax</i>	921	FNTIEEAKEGRCIYNNMKAFIRYLISSNIGEVASIFLTAL
<i>P. yoelii</i>	838	FNTIVEAIKEGRCIYNNMKAFIRYLISSNIGEVASIFITAI
<i>P. berghei</i>	843	FNTIVEAIKEGRCIYNNMKAFIRYLISSNIGEVASIFMNAI
SERCA1	740	FSTIVAAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAA

M7

<i>P. falciparum</i>	1028	LTLLRYIIIGTYVGIATV
<i>P. vivax</i>	997	LTLLRYIVIGTYVGVATV
<i>P. yoelii</i>	914	LTLLRYIVIGTYVGIATV
<i>P. berghei</i>	919	LTLLRYIIIGTYVGIATV
SERCA1	815	WLPFRYMAIGCYVGAATV

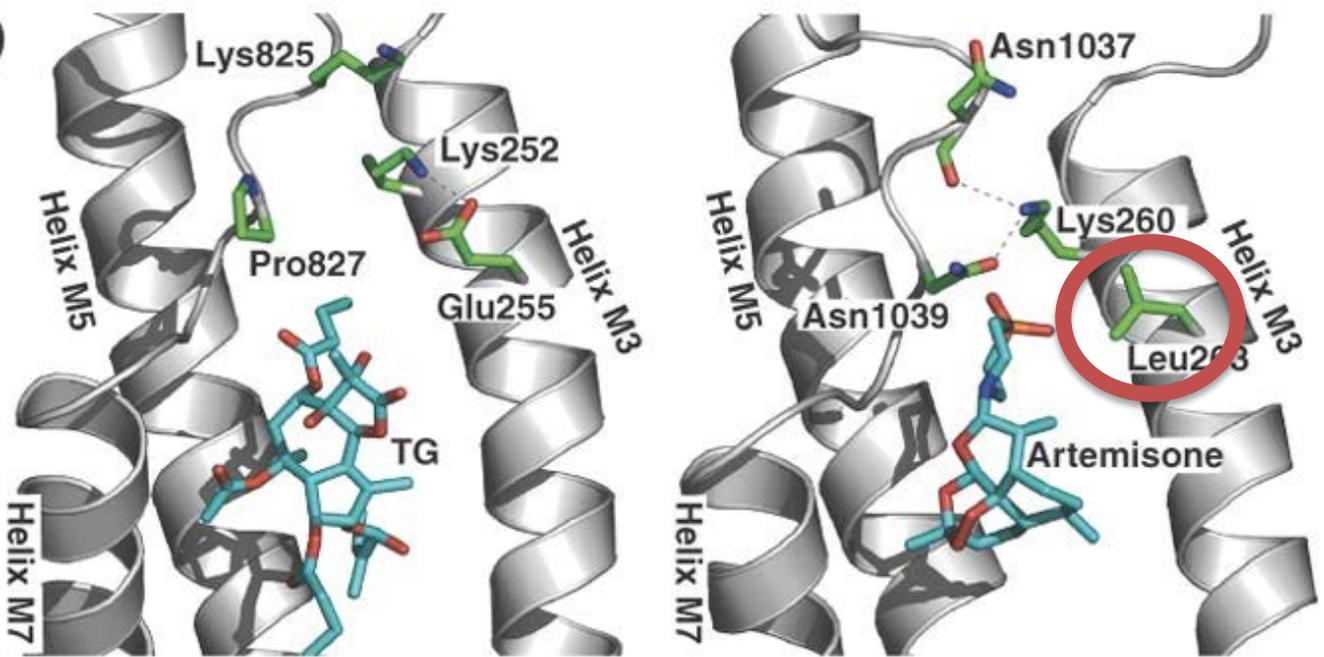
b

Table 1

Nature Structural & Molecular Biology 12, 628 - 629 (2005)

Published online: 5 June 2005; | doi:10.1038/nsmb947

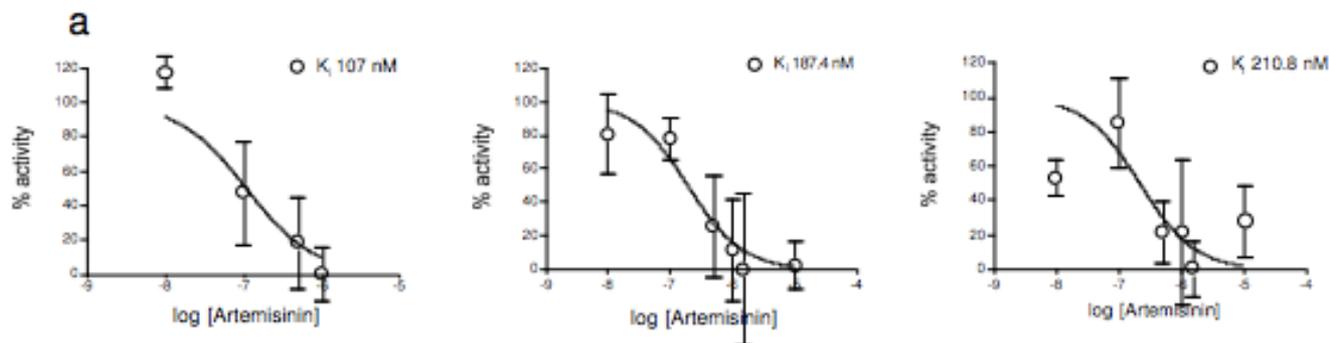
A single amino acid residue can determine the sensitivity of SERCAs to artemisinin

Anne-Catrin Uhlemann, Angus Cameron, Ursula Eckstein-Ludwig, Jorge Fischbarg, Pavel Iserovich, Felipe A Zuniga, Malcolm East, Anthony

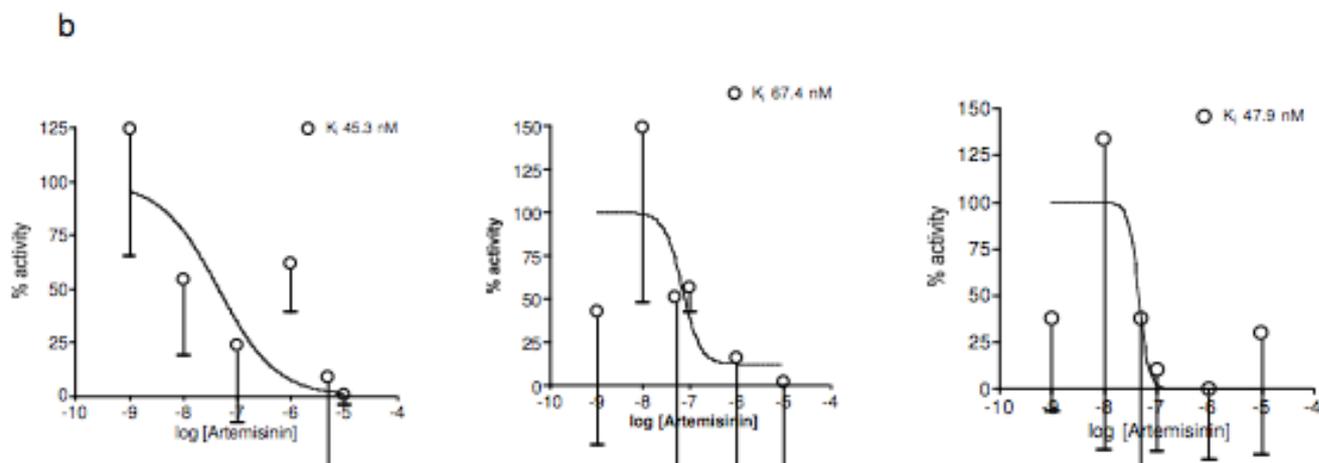
Sequence	Artemisinin K_i (nM)
PfATP6	
Leu263 (wild type)	$169 \pm 31^a / 4.4 \pm 1.7^b$
L263A (<i>P. vivax</i>)	63 ± 12^a
L263S (<i>P. berghei</i>)	530 ± 84^a
L263E (mammalian)	>50,000
L263D	>50,000
L263K	>50,000
L263Q	552 ± 143
F264L	$4,150 \pm 1,850$
I89T	122 ± 13
SERCA1	
E255L (<i>P. falciparum</i>)	314 ± 109^c
Orthologs	
PvSERCA	7.7 ± 4.9
PbSERCA	$5,660 \pm 2,330$

In en senere rettelse: originaldata fremlægges

activity in the presence of an artemisinin inhibitor, normalised with respect to values that are obtained without presence of inhibitor.



(a) Inhibition of PfATP6 Ca^{2+} -ATPase activity by artemisinin with data from 3 independent experiments.



(b) Inhibition of PfATP6L263A by artemisinin, with inclusion of 2 possible outlying values (at 1nM). Results from 3 experiments are presented here (4 experiments were analyzed in the original paper).



Reappraising the effects of artemisinin on the ATPase activity of PfATP6 and SERCA1a E255L expressed in *Xenopus laevis* oocytes

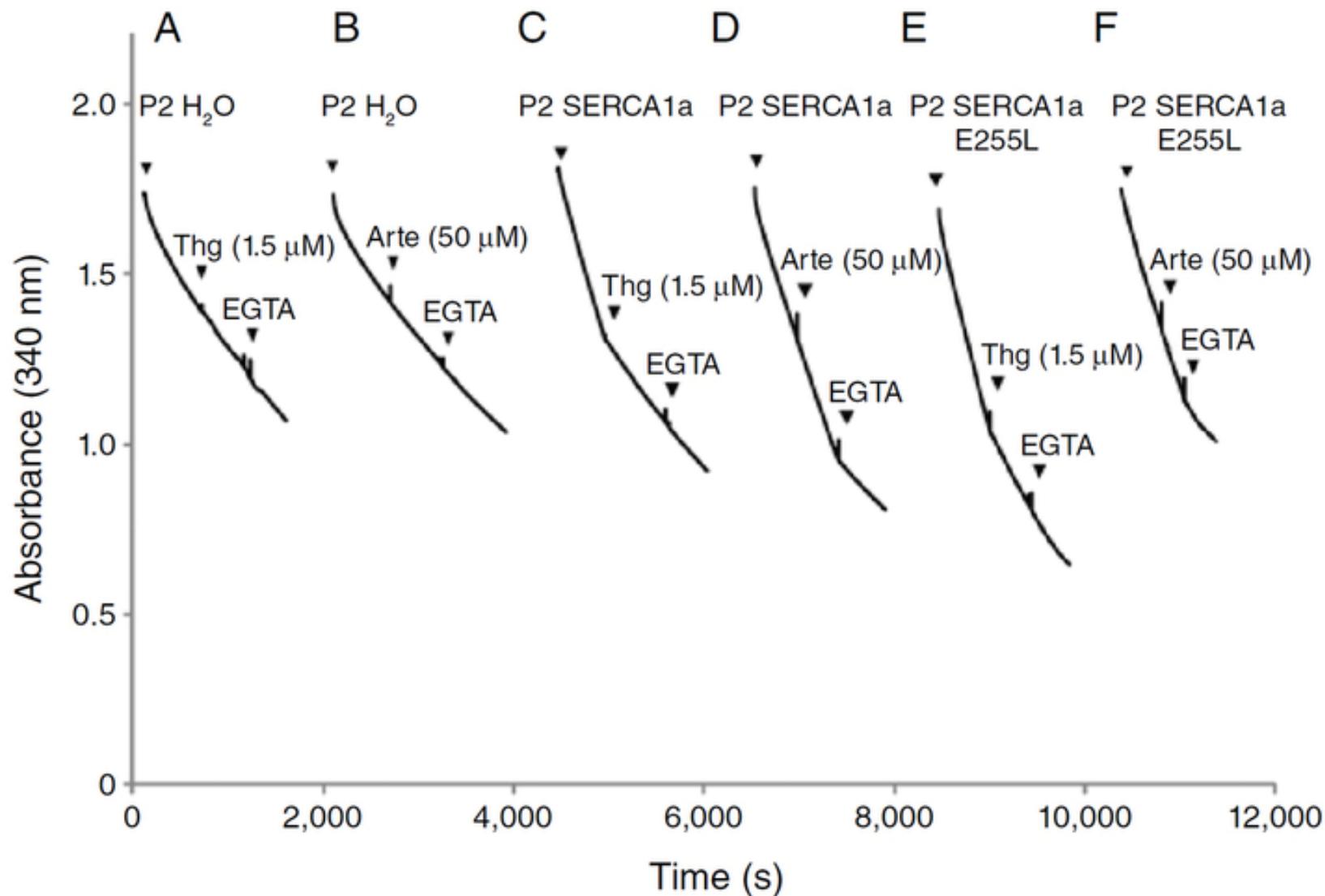
[Stéphanie David-Bosne](#), [Michael Voldsgaard Clausen](#), [Hanne Poulsen](#), [Jesper Vuust Møller](#), [Poul Nissen](#) & [Marc le Maire](#)

[Affiliations](#) | [Corresponding authors](#)

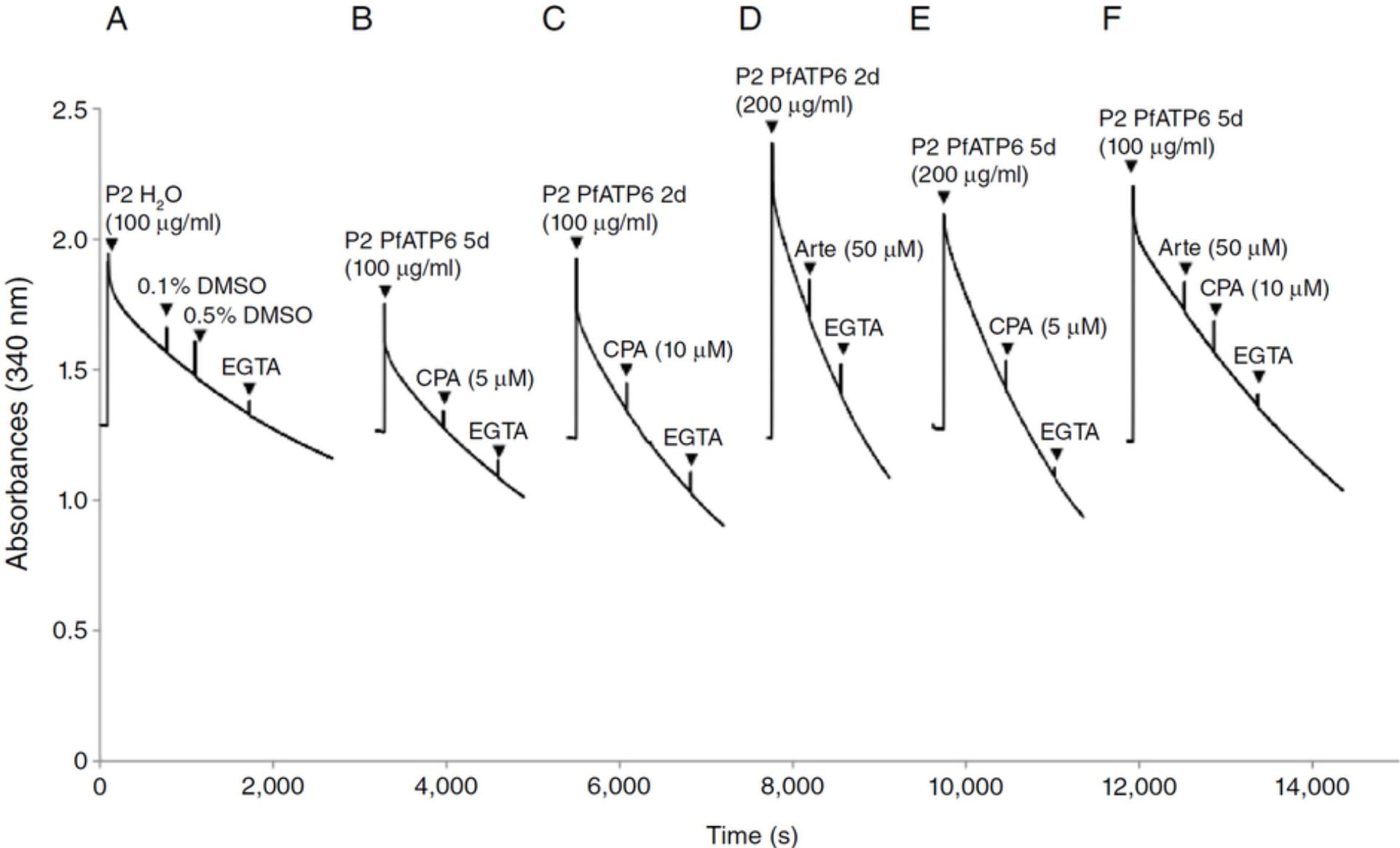
Nature Structural & Molecular Biology **23**, 1–2 (2016) | doi:10.1038/nsmb.3156

Published online 06 January 2016 | Corrected online **13 January 2016**

Vi kan ikke måle en effekt af artemisinin på SERCA



..eller på PfATP6



Hvordan virker det så? Wiki:

Mechanism of action [\[edit \]](#)

As of 2015, the mechanism of action of artemisinins was not known, but the most widely accepted theory was that they are first activated through cleavage after reacting with **haem** and **iron(II) oxide**, which results in the generation of **free radicals** that in turn damage susceptible proteins, resulting in the death of the parasite.^{[36][37]} In 2016 artemisinin was shown to bind to a large number of targets suggesting that it acts in a promiscuous manner.^[38]

Hvordan virker det så? WHO:

In late 2013, researchers identified a molecular marker: mutations in the Kelch 13 (K13) propeller domain were shown to be associated with delayed parasite clearance in vitro and in vivo. The molecular marker could allow for a more precise mapping and monitoring of the geographical distribution of resistance. It could also enable a retrospective mapping of possible resistance in a large number of settings. WHO is working with researchers, national malaria programmes and other partners – within and outside of the GMS – to map the presence of artemisinin resistance. Meanwhile, therapeutic efficacy studies remain a central tool for monitoring the efficacy of nationally recommended antimalarial treatments in all countries.



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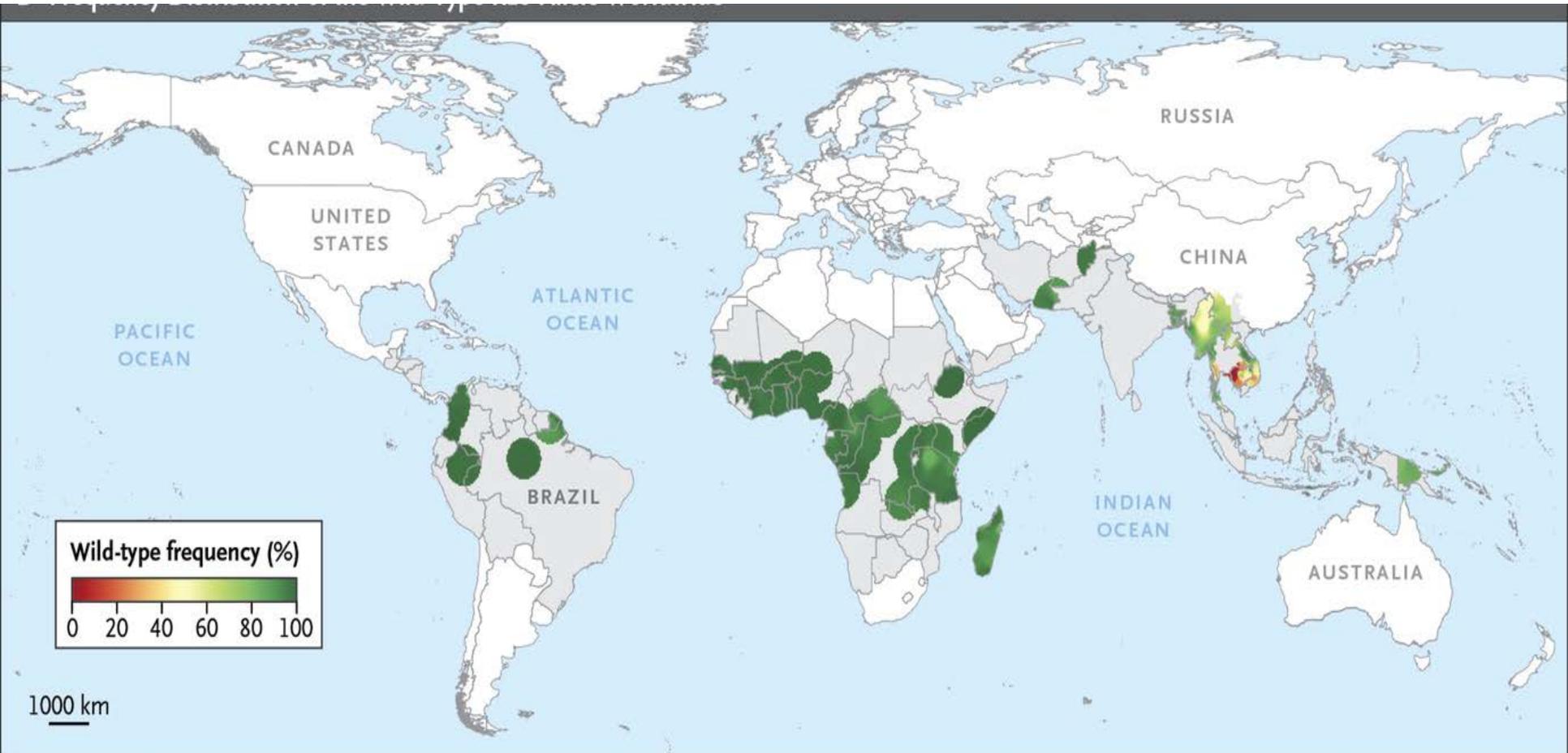
ORIGINAL ARTICLE

A Worldwide Map of *Plasmodium falciparum* K13-Propeller Polymorphisms

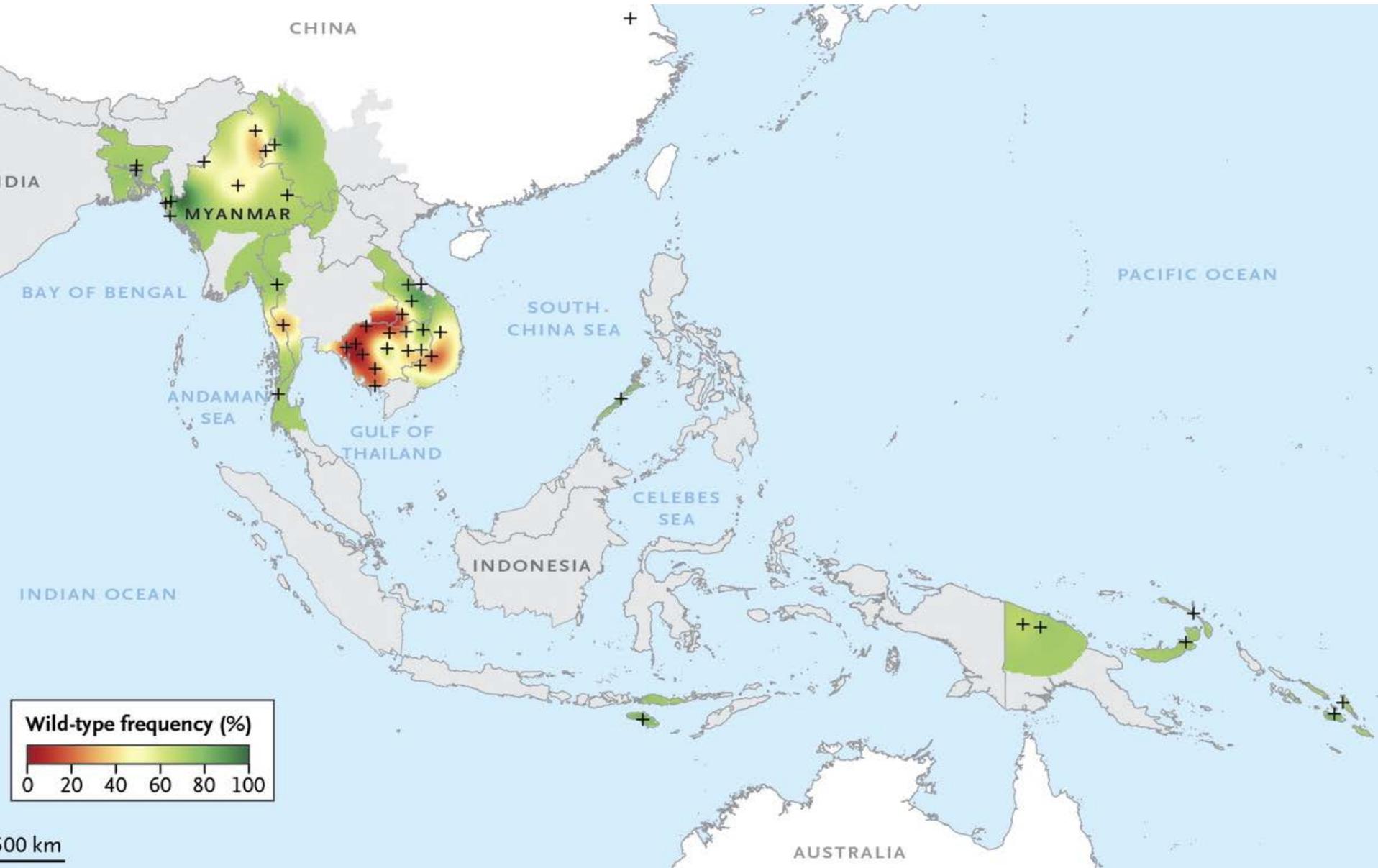
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Valentine Duru, M.Sc., Eric Legrand, Ph.D., Jean-Christophe Barale, Ph.D., Barbara Stokes, B.Sc., Judith Straimer, Ph.D.,
Benoit Witkowski, Ph.D., David A. Fidock, Ph.D., Christophe Rogier, M.D., Ph.D., Pascal Ringwald, M.D., Frederic Ariey,
M.D., Ph.D., and Odile Mercereau-Puijalon, Ph.D., for the KARMA Consortium*

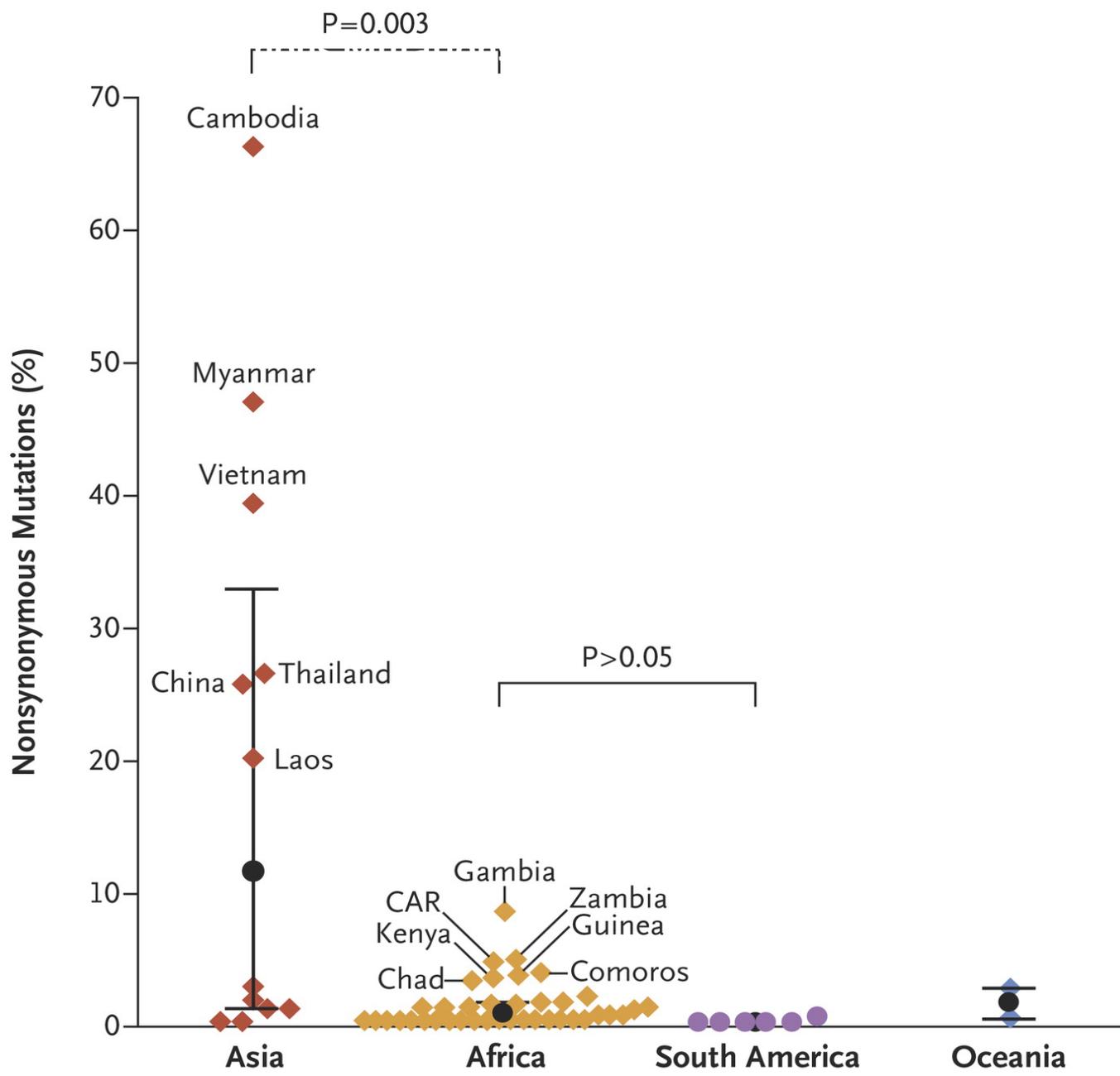
N Engl J Med 2016; 374:2453-2464 | June 23, 2016 | DOI: 10.1056/NEJMoa1513137

Frequency Distribution of the Wild-Type K13 Allele



Frequency Distribution of the Wild-Type K13 Allele



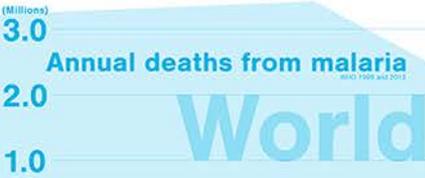


WHO: artemisinin-kombinationsterapi stadig effektivt

Currently, even if patients are infected with artemisinin-resistant parasites, nearly all patients treated with an ACT are fully cured provided that the partner drug is highly efficacious in that geographical area. In the absence of partner drug resistance, artemisinin partial resistance rarely leads to treatment failure. Furthermore, there is no evidence that artemisinin partial resistance alone has resulted in an increase in malaria morbidity and mortality in the GMS. Nevertheless, the proportion of treatment failures increase when both resistance to artemisinin and to ACT partner drugs are present, compared to resistance to the partner drug alone.

PERSISTENT BATTLES WITH MALARIA

Fighting not only with mutating parasites but also with drug and insecticide resistance



1930

- Malaria was once prevalent throughout much of the inhabited world.
- Around 2 million deaths occurred from malaria each year, most in the Asian and the Pacific tropics, and fewer in Africa.

1960

- National malaria control campaigns were initiated or intensified in the most affected countries starting from the Middle East through India and South-East Asia. DDT spraying and antimalarial drugs reduced malaria incidence and mortality.
- Effective (public health) campaigns eliminated malaria from Canada, US, Europe, and Russia.

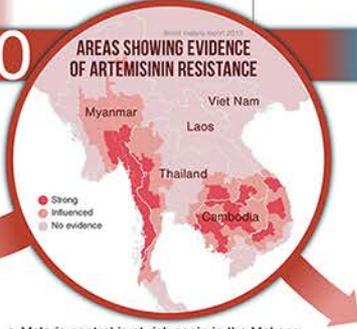
1990

- Malaria prevalence resurged in tropical countries due to the relaxed control efforts and increasing antimalarial drug and insecticide resistance.

Africa

2010

- 2003 Global fund support began for malaria control
- Prevalence has fallen as a result of vector control effort and use of new artemisinin combination drugs (ACTs)



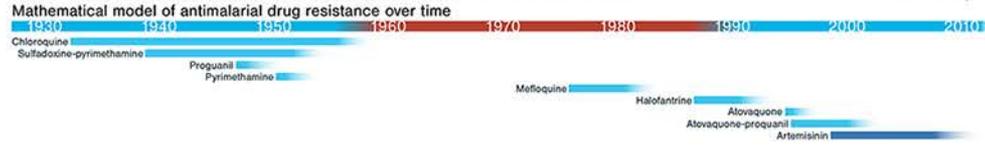
- Malaria control is at risk again in the Mekong subregions. *P. falciparum* (most lethal strain of malaria) resistance to artemisinin was first identified on the Thailand-Cambodia border. The resistance is now present in five countries.

* Counterfeit and substandard medicines are also accelerating the rate of resistance development. More active countermeasures, stronger legislation, and better surveillance are needed.
(Palisades, & White et al, January 2014)

MOVING FORWARD

- Malaria control is in need of heroic efforts, funding, and political commitment
- International research groups are working on primary healthcare technologies and community based solutions to eradicate Malaria for the whole world

ANTIMALARIAL DRUG EFFICACY HAS DROPPED DUE TO GENETIC MUTATIONS AND OTHER FACTORS



AS OF NOW, ACTS ARE THE MOST EFFECTIVE AND DEPENDED ON MEDICATION FOR MALARIA

