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wellcome^{trust}

Chemosensitisation of malaria parasite by probenecid

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Background

Antimalarial resistance:

burgeoning problem.....

even against Artemisinin



More than ever... new drugs are needed....

In malaria....

Current strategies in drug discovery against malaria

Antimalarial discovery= **2 old orthodox approaches.....**

1. from **natural product** to drugs
2. **Synthetic or semi-synthetic drugs** from existing drugs or not

But human pharmacopeia..

In addition to the 2 old approaches...

-**New use of old drugs (with anticancers, methotrexate in Phase I) [Poster]**

- Use of modulators of activity to increase drug efficacy

Modulator of efficacy, chemosensitisation, potentiation or reversal of resistance

Modulation or Chemo-sensitisation: combination of 2 drugs

Drug A (active, less active or resistant)

Drug B (not active) but makes **drug more A active**

Drug A= active or less active  **potentiation**

Drug A= resistant  **Reversal of resistance**

Reversal of resistance.. from anticancer drugs...

verapamil (VPM), cyclosporine A (CsA) ect...
(higher dose required, toxic *in vitro*)

(first generation)



dex-verapamil, and Valspodar (analog of VPM and CsA)
(better, but still toxic)

second generation



Tariquidar, Elacridar
(better safety profile, but efficacy not proven yet,
still underway, Phase III)

Third generation

While new compounds being tested as chemosensitisers..

Existing drugs are investigated as well:

For instance, in vitro chemosensitisation:

mefloquine, quinine, quinidine, pyronaridine, primaquine

Quinine in vivo: 2 clinical evaluations (Phasell/III)

(encouraging results)

other trials underway.....



Reversal of resistance or Chemo-sensitisation:

important in cancer research in spite of the richness of pharmacopeia

Chemosensitisation in malaria

From cancer research...

Verapamil /analogs:

chemosensitise chloroquine (CQ)



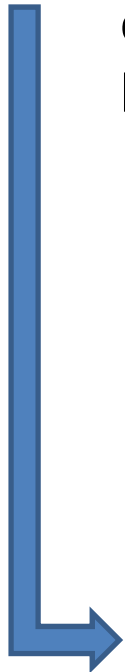
but high dose needed *in vivo* = risk of toxicity



clinical trials conducted in Nigeria: some good results
but in **low CQ resistance**



No attempts **in high CQ resistance areas**



No exploited...

higher doses (toxic) of reversing agents are required

Probenecid (PBN): a ucosuric agent..

In cancer research: PBN increases antifolate activity

in vitro: well studied with methotrexate [MTX]

in vivo: PDX, analog of MTX, in combination with PBN to treat cancer

In malaria: increases pyrimethamine/sulfadoxine (SP) activity

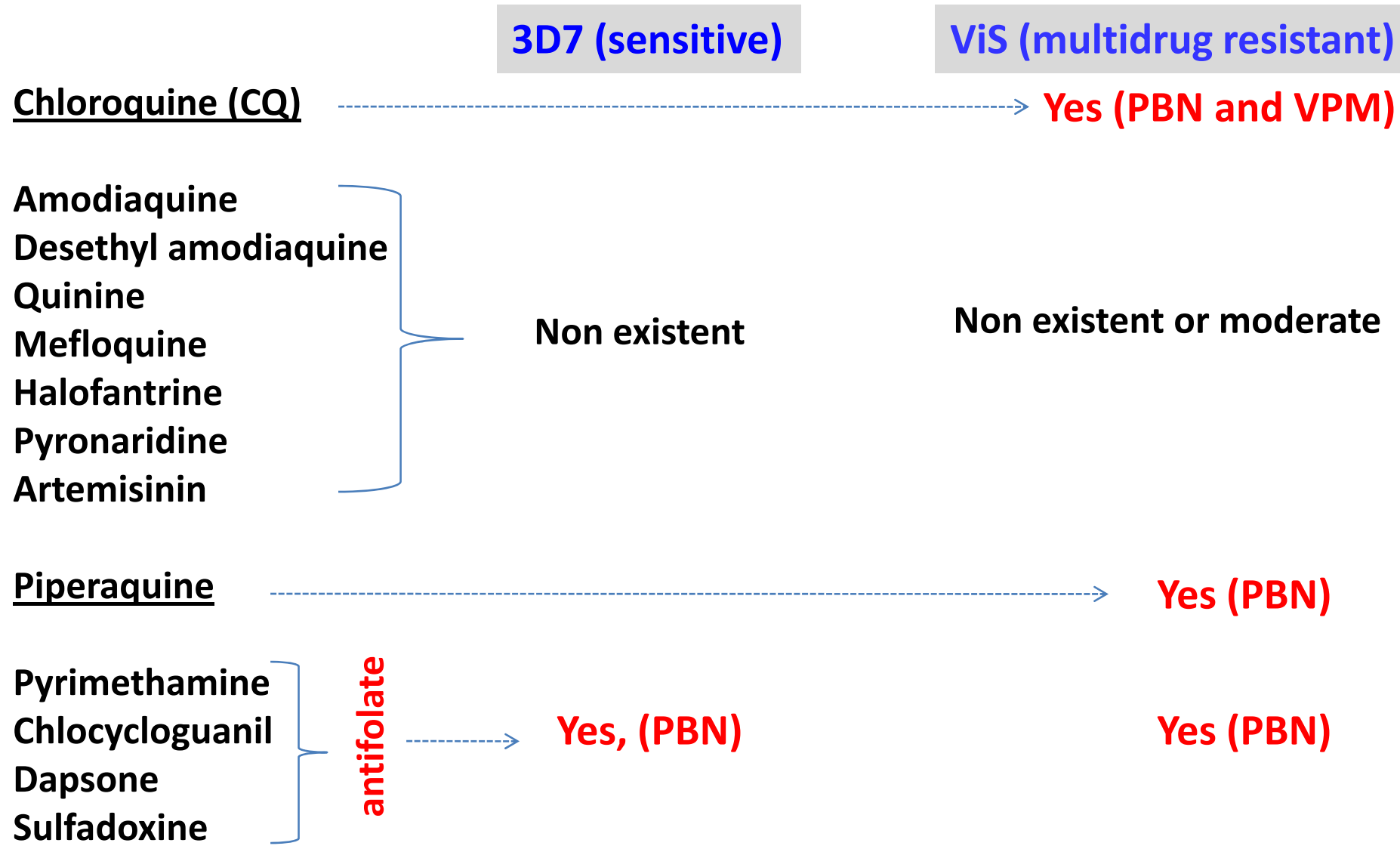
in vitro (by our group) [Nzila et al. AAC 2003 ,47:p2108; Nzila et al. Trends Par 2003 9:479-]

in vivo (in Nigeria) in children treated with SP

In malaria: reverses CQ resistance **in vitro**

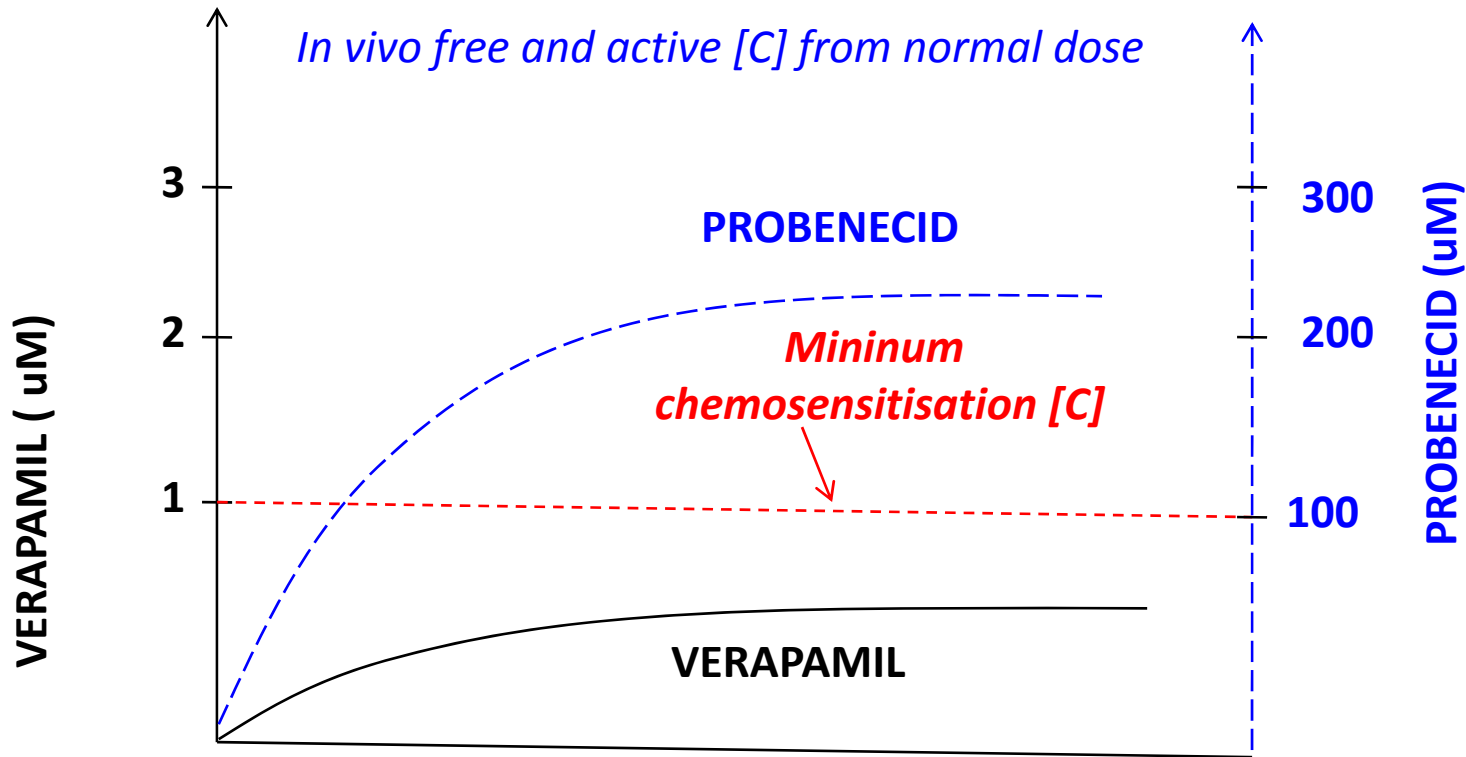
Potential of **Probenecid (PBN)** to chemosensitize other antimalarials.
Verapamil (VPM) as control.

Method: In vitro activity alone and in presence of **PBN** or **VPM**



Chemosensitisation:

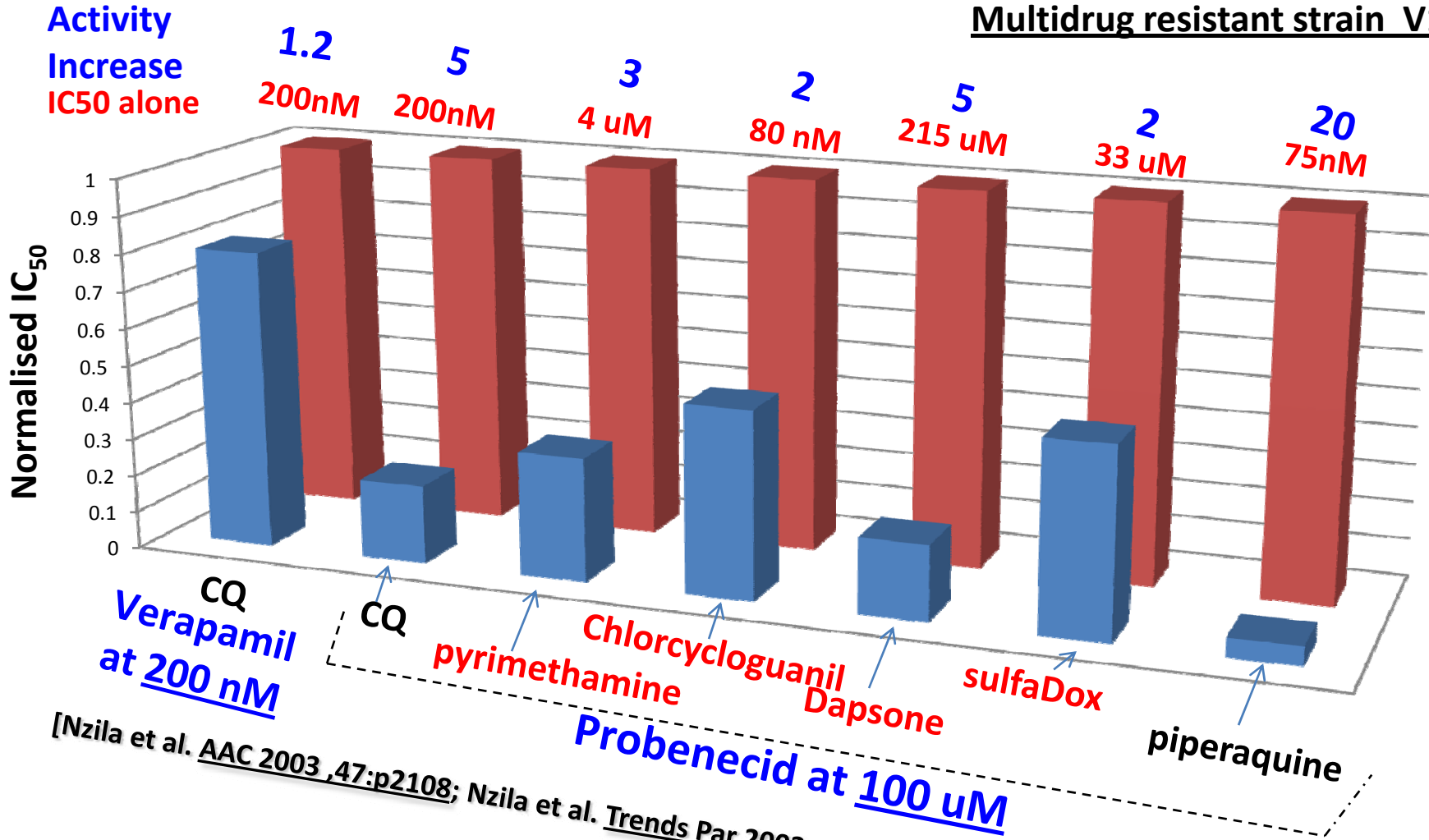
Clinically relevant if adequate drug concentration can be achieved in vivo



In vivo level of chemosensitisers (free drug) after the use of normal dose

- Probenecid:**
- High **in vivo [C]** can be achieved when normal dose
 - **[C] > 100 μM** , high enough to reverse resistance

Multidrug resistant strain V1S



[Nzila et al. AAC 2003 ,47:p2108; Nzila et al. Trends Par 2003 9:479-87; Masseno et al. AAC 2009]

PBN: **better pharmacokinetics, high dose can be used, cheap**

 **A better reversing agent... but not successful in getting funds**

Feedback from sponsors: Why spending money on failing drugs?

in cancer

many drugs are available but **work on chemosensitisation**

In bacteria

amoxicillin and **clavulanic acid** (reversing agent) = Augmentin®

 **Reversing agent + Antimalarial:**

if safe and cheap... no reason why not in malaria

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