

# Selection of a New Artemisinin Antimalarial: Efficacy is Not the Most Important Factor

*Speaker: Prof. Richard K. Haynes*

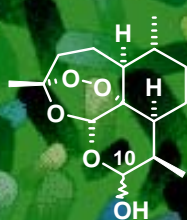
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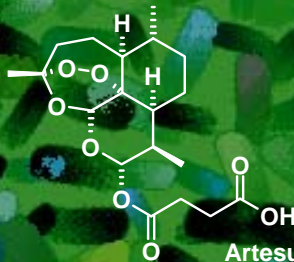
**Time: 1100 – 1200**

**Venue: S4-05-SR**

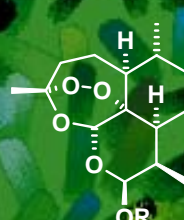
The antimalarials dihydroartemisinin (DHA), artesunate and the ethers have problems of chemical and metabolic instability, and neurotoxicity. Artesunate is hydrolysed in minutes *in vivo* to DHA, and the ethers are metabolized to DHA. Neurotoxicity, especially of DHA, shows up in *in vivo* and *in vitro* assays, and recent reports enhance the suspicion of an emerging problem in humans. In any event, toxicity must be considered within normal drug regulatory guidelines for registration of new artemisinins.



Dihydroartemisinin (DHA)



Artesunate



R = Me; Artemether  
R = Et; Arteether

In preparation of the new artemisinins, little attention has been paid to enhancement of systemic properties in relation to efficacy and toxicity. For uptake to occur through a membrane, a drug must possess limiting aqueous solubility, and should not be overtly lipophilic. Best systemic activity is displayed in the 'moderate' lipophilicity range (Log P ~ 1.5-3). The ethers are lipophilic (arteether Log P 3.99). Although artesunate is more polar (Log P 2.77 at pH 2), it is >99% ionized at pH 7.2, and as such is unstable; uptake of the neutral artesunate from the intestinal tract will be minimal. The connection between lipophilicity and toxicity was made some time ago for artemisinins - whilst lipophilic artemisinins possess better activities against malaria, these are more neurotoxic. Therefore, lowering of Log P through attachment of polar groups should be conducted deliberately, with the aim of attenuating neurotoxicity and enhancing systemic properties. In the lecture, we will disclose examples of artemisinins which appear not to be neurotoxic in validated assays, but still possess very good antimalarial efficacies. The lecture will conclude with an overview of mechanism of action in relation to development of the drug against other targets.