Non-natural myristate analogues: Synthesis and biochemical characterization of their activity in protozoan parasites

Inadequate and antiquated drugs for treating a wide range of neglected tropical diseases are limiting their eradication. Despite there being some research into the potential of analogues of myristate as anti-trypanosomal agents, the biochemical characterization of their mode-of-action is largely unreported, which limits their use as potential therapeutics. This research is focused on characterising the phenotypes of known/novel myristate analogue effects in *Trypanosoma brucei*. The use of complimentary small molecule probes based upon myristate to identify compound protein targets. These myristate analogues showed EC_{50} values of <10 μM in the presence of 10 % foetal bovine serum (FBS) against *Trypanosoma brucei*, but significantly lower EC_{50} values (nanomolar) in more physiologically relevant (5%) FBS conditions. Through a series of gas chromatography mass spectrometry (GC-MS) based biochemical characterizations and metabolomic analysis, these myristate analogues were shown to sequester/ accumulate as probable acyl-CoA species within *T. brucei*. A metabolomics approach confirmed the elongation of one fatty acid analogue, 10-(propoxy)decanoic acid, **O11**, which is a novel finding for this known myristate analogue. Herein there is also evidence for the likely interaction of myristate analogue acyl-CoA species with the *N*-myristoyltransferase enzyme. Using bi/mono-functional molecular it was found that these myristate analogues are used for the lipidation of a number of proteins, with the likely targets being the inositolphosphoceramide synthase (Tb927.9.9380) and the flagellar Ca^{2+} binding protein (Tb927.8.5460), the knock down of the latter giving the same unusual detached flagellar as treatment with these myristate analogues.