Non-natural myristate analogues: Synthesis and their potent, selective activity upon bloodstream *T. b. brucei*

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Inadequate and antiqued drugs for treating sleeping sickness, a neglected tropical disease caused by the protozoan *Trypanosoma brucei* (*T. brucei*), remains a persistent problem across many developing countries. One chemotherapeutic target, the N-myristoyltransferase (NMT) has received significant attention in recent years and has been validated as drug target against *T. brucei;* ablating the NMT gene led to cell death and is thus essential for parasite survival. By synthesizing trypanocidal myristate analogues, it is hoped that these structural mimics will be taken up and utilised by *T. brucei* NMT, leading to the interference and disruption of their downstream metabolic pathways. Additionally, fatty acid elongation and repurposing is likely to be disrupted upon the treatment of non-natural analogues, potentially leading to toxic effects. This research mainly describes the chemical synthesis of myristate analogues based on the 14:0 fatty acid chain with some compounds showing EC_{50} values of <10 μM in the presence of 10 % foetal bovine serum (FBS) and significantly lower EC_{50} values in FBS depleted environments. Initial analysis of free fatty acid and phospholipid species via MS techniques has highlighted significant differences in the abundances of certain species. Tandem MS/MS can be used to identify the specific changes in individual phospholipid species. This analysis is complemented by general non-specific metabolomics on whole cell samples to further identify biological pathways affected by these compounds. To directly determine the extent at which the NMT enzyme is affected or inhibited, TbNMT protein was expressed and purified to allow thermal shift assays and secondary peptide activity assays to be carried out. The synthesis and use of bi-functional probes for drug localisation studies is also explored in this research in the hopes of further elucidating drug localisation and thus potential target identities.

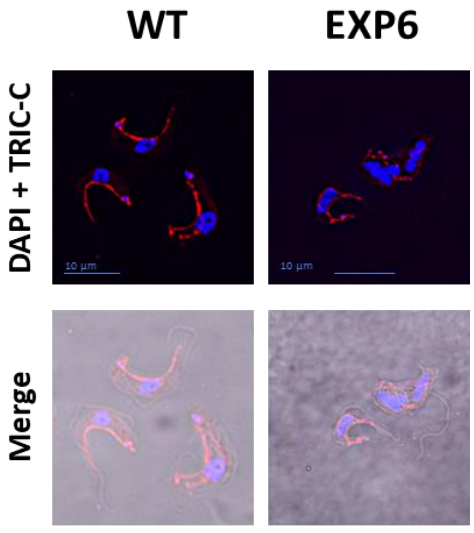

Figure 1: Wild type vs drug treated cells