Towards nucleoside analogues with potent activity against *Trypanosoma* and *Leishmania* species.

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One of the main barriers between the identification of potential lead compounds against parasite-borne diseases and their clinical development as potential new drugs is that the development cost for a possible drug against a single neglected disease is deemed to be too high relative to the potential benefits for the manufacturer. Adenosine analogues with potent activity against veterinary trypanosomiasis have been identified [1–3], but most are much less active against *Leishmania* species. We reasoned that the most likely reasons for the uneven activity were (a) differences in activation by adenosine kinase (AK) or (b) differences in adenosine transporters, which are NT1 in *Leishmania* and P1 and P2/TbAT1 in *Trypanosoma brucei brucei* [2,4].

We have created a number of investigative cell lines, including *L. mexicana* ΔLmexAK, and ΔLmexAK expressing TbbAK to investigate whether *Leishmania* AK could be the factor limiting sensitivity to adenosine analogues. Equally, we created ΔLmexNT1 (*null* adenosine uptake) and *T. brucei* ΔTbAT1 as well as ΔLmexNT1 expressing *T. congolense* and *T. vivax* P1-type adenosine transporters. The SAR of the AKs were investigated by determining the EC_{50} values for adenosine analogues against the various cell lines, transporters and AKs. Docking studies were conducted comparing the poses of analogues in the *Leishmania* and *Trypanosoma* adenosine kinases. Detailed transport assays of nucleoside analogues as inhibitors of LmexNT1 are being conducted.

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