NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

BIOLOGY COLLOQUIUM

Friday, 18 August 2017 | 4pm | DBS Conference Room 1

Hosted by Professor R M Kini

A Structure-Guided Approach towards the Design of Drugs for Neglected Tropical Diseases

By **Wilhelmus Hol**

Professor, Department of Biochemistry,
University of Washington, Seattle WA, USA

There is a great need to develop novel drugs for treating patients suffering from a range of Neglected Topical Diseases. Three projects targeting tRNA synthetases, essential enzymes from Trypanosomatids, the causative agents of leishmaniasis, sleeping sickness and Chagas disease across the globe, are highlighted. Protein synthesis depends on the arrival of charged tRNAs at the ribosome. The attachment of the proper amino acid to a specific tRNA is carried out by tRNA synthetases in an ATP dependent fashion. Since protein synthesis is crucial for all organisms including parasites, the reaction catalyzed by tRNA synthetases is essential for life. Inhibiting this process is therefore in principle an interesting avenue for arriving at compounds which can stop parasite growth. Here we describe approaches taken in projects which aim to arrive at inhibitors, and eventually new drugs, of tyrosyl tRNA synthetase from *Leishmania donovani*, and the methionyl-tRNA synthetases from *T. brucei* and *T. cruzi*. The *T. brucei* MetRS studies revealed unexpected conformational changes upon inhibitor binding. The methionine pocket is considerably enlarged by one ring system of the inhibitors and, a second, auxiliary, pocket (AP) is even absent before inhibitor binding. The AP is most likely the result of conformational selection upon binding. Detailed analysis of inhibitor contacts in the AP was followed up by synthesis of variants of initial inhibitors, where precise substituents were added to the ring occupying the AP. It appeared that small differences in substituent size have major consequences for affinity and EC_{50} values. MetRS inhibitors were obtained with EC_{50} values for *T. brucei* growth in the single digit nM range. Building on the studies in *T. brucei* MetRS, promising inhibitors of the homologous *T. cruzi* MetRS were obtained with low EC_{50} values for *T. cruzi*. Structural information can clearly be useful in the design of new inhibitors but this is not trivial, in particular when conformational changes are occurring. Moreover, the effect of substitutions on pharmacological properties remains challenging. A dedicated and sophisticated multi-disciplinary approach is essential to be successful.