Structural biology in parasitic infectious diseases

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Infectious diseases continue to impede social and economic progress in the developing countries, disproportionately affecting poor and marginalized populations. Alone, the ten diseases included in the TDR initiative of the World Health Organization (malaria, tuberculosis, schistosomiasis, lymphatic filariasis, onchocerciasis, leishmaniasis, Chagas disease, African trypanosomiasis, leprosy, and dengue) cause 3 million deaths per year and account for the loss of over 90 million DALYs (Disability-Adjusted Life Years, a quantitative estimate of the impact of disease in the loss of healthy life years). On the other hand, the currently available chemotherapy is extremely limited with drugs that were predominantly developed in the first half of last century, presenting significant risk due to side effects. Additionally, the widespread upsurge of microorganisms resistant to the available drugs has been alarming, whereas the development of new alternatives for treatment and prevention has been minimal. Of the 1393 new chemical entities (NCE) that reached the pharmaceutical market between 1975 and 1999, only 16 were indicated to the treatment of tropical diseases and tuberculosis. Tropical diseases affect primarily the poorest populations, which is not an attractive market for the international pharmaceutical companies, therefore representing a challenge for the Medicinal Chemistry of developing countries, Brazil included. In this talk we will present our integrated experimental approach to this goal, which includes cloning and overexpression of parasitic enzymes, their crystallization and X-ray crystallography studies, rational drug design, synthesis and extensive screening and testing of both synthetic and natural products compounds obtained from the Brazilian biodiversity. In the past years, a dozen different proteins from tropical parasites had their structures elucidated in our lab, related to Chagas disease, leishmaniasis, schistosomiasis, sleeping sickness and malaria. Also, in an on-going program to screen natural products libraries in the search for new potential inhibitors, a series of promising compounds were identified and subsequently improved by structure based drug design, QSAR techniques and conventional and combinatorial chemistry. We will conclude by focusing on the enzyme GAPDH from *T.cruzi*, of which we have 6 different structures, the apo- and holo- forms, one structure with only one NAD+ bound to the tetrameric particle, and three structures of complexes with inhibitors. This plethora of structural information contributes to a better understanding of the biochemical mechanism of this enzyme.

FAPESP, CNPq, FINEP and LNLS