

PHENOTYPIC HIGH-THROUGHPUT SCREENING FOR KINETOPLASTIDS

L. Freitas-Junior¹, J. L. Siqueira-Neto¹, G. Yang¹, J. Jang¹, J. Cechetto¹, S. Moon¹, A.

Genovesio¹, J. Ioset², E. Chatelain²

¹Center for Neglected Diseases Drug Discovery, Institut Pasteur Korea, Seongnam-shi, Gyeonggi-do, Sth Korea

²Drugs for Neglected Diseases initiative, Geneva, CH- 1202, Switzerland

In Institut Pasteur Korea (IPK), the Center for Neglected Diseases Drug Discovery (CND3) develops highcontent/ high-throughput screening assays (HCS/HTS) for finding new drugs for the treatment of Leishmaniasis and Chagas disease. Using a technically challenging whole-cell-based approach, we have screened 200,000 drugs that impair the growth of the most deadly species causing visceral leishmaniasis, *Leishmania donovani*, inside their natural host cell, the human macrophage. Among these compounds, 179 were selected as active, inhibiting parasite growth while not harming the macrophage host cell. We have also developed a whole-cell model assay for discovery of compounds active against *Trypanosoma cruzi*, the causative agent of Chagas disease. Two different *T. cruzi* strains, Y and Dm28c, representing the two *T. cruzi* groups, were used in the screening of 4,000 compounds, showing that these two strains differ on their infectivity and spectrum of response to the 4,000 compounds. Now both leishmaniasis and Chagas assays are being used for screening an additional library of 150,000 compounds in collaboration with Drugs for Neglected Diseases initiative (DNDi) and Pfizer, thus further increasing the number of potential drug candidates in the pipeline of Chagas and leishmaniasis drug discovery. In parallel, we developed a high-content assay for kinetoplast-directed drug discovery for *Leishmania* and *T. cruzi* parasites. The kinetoplast is a single mitochondrion, exclusive to order Kinetoplastida (*Leishmania* and *Trypanosoma cruzi*, among other parasites) and contains a number of excellent chemotherapeutic targets that are very unlikely to be found in the human host. The hits found in the whole-cell assays for *T. cruzi* and *Leishmania* will be further tested in the kinetoplast assay for assessment of their potential kinetoplasttargeting mechanism of action.