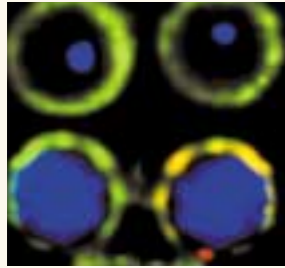


Malaria

Malaria is caused by single-celled *Plasmodium* parasites and is the cause of over 1 million deaths per year worldwide. The disease manifests itself in several debilitating ways, from high fever and anemia to deep vascular blockage of blood flow in vital organs such as the brain or placenta during pregnancy. Although there are anti-malarial drugs available, malaria treatment faces today the serious issue of parasite resistance to chemotherapy. There is an urgent need of developing new drugs, mostly acting through new mechanisms of actions and thus overcoming existing resistance.



Courtesy to DNDI

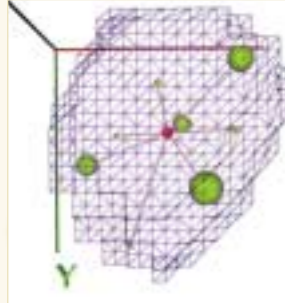
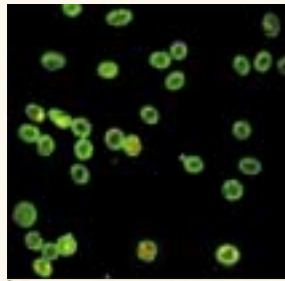


IP-Korea

Finding new scaffolds active against *Plasmodium* growing in vitro is relatively easy. However, this strategy does not prioritize the finding of new targets so badly needed in malaria drug discovery and development. In IP-Korea, we opted to screen for drugs that block the invasion process, which is mandatory pathogenic process and essential to parasite survival. During invasion, free parasites in the human bloodstream enter circulating red blood cells in order to perpetuate the parasite's cycle in the host. In spite of its importance to parasite survival and disease progression, currently no drugs target the invasion process. A phenotypic cell-based assay, relying on automated high-throughput microscopy and image analysis, was developed in IP-Korea in order to find such new promising drugs.

To achieve such complex task, we are developing in IP-Korea a software that is capable of automatically recognize the life cycle stage of the *Plasmodium* parasite by analyzing the size of the parasites nucleus.

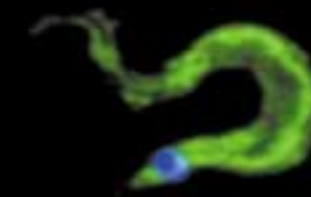
- Throughput: 120,000 compounds/month;
- Invasion of the host cell is an essential step for the malaria parasite. Due to its complexity this process could never be tackled for drug discovery in high-throughput. We developed new and unique approach to search for drugs blocking invasion of malaria parasites.
- The only image-based phenotypic drug screening for malaria



Institut Pasteur Korea

Sampyeong-dong 696, Bundang-gu, Seongnam-si, Gyeonggi-do 463-400, Korea
T 82-31-8018-8000 F 82-31-8018-8010 <http://www.ip-korea.org>

Neglected Diseases



Institut Pasteur Korea

Bringing The Most Neglected to The Main Stage

Leishmaniasis, Chagas Disease and Malaria are examples of neglected infectious diseases responsible for over 1 million deaths each year. Currently available drugs are mostly ineffective due to resistance in the causative parasites, and in some cases the drugs themselves are potentially deadly for patients. In this context, the discovery of new drugs is urgently needed.

The Pasteurian mission has always had a deeply humanistic endeavour, helping the needs of public health for over 130 years. Backed by the rich history of Institut Pasteur and with screening capabilities matching the best pharma companies, Institut Pasteur Korea emerges ideally positioned to tackle neglected diseases.

Consequently, using our sophisticated high content phenotypic screening approach we are able to search for new drugs. Using living cells based approaches, we designed assays that allow selection of compounds that have potent activity against the pathogens and are at the same time not toxic for the human cells, in a faster pace than obtained by traditional pharma.

Institut Pasteur Korea is tackling neglected disease drug discovery in partnership with leading international agencies, such as the Drugs for Neglected Diseases *initiative* (DNDi). The focus of DNDi is to finance the development of new and improved treatments for neglected diseases which do not interest market driven pharma R&D. Our close association with DNDi is aimed at bringing new hope to millions of individuals who suffer from neglected diseases worldwide.

* Numbers on some of the Neglected Diseases:

- Leishmaniasis: 200.000.000 people at risk
- Chagas Disease: 100.000.000 people at risk
- Malaria: 3.200.000.000 people at risk

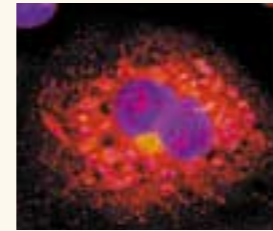
Leishmaniasis

Leishmaniasis is the collective name of diseases with broad manifestations and impact on human life in 88 countries around the world. The disease is caused by single-celled parasites from the genus *Leishmania* and it is estimated that 12 million people are currently infected worldwide. The disease ranges from skin lesions to life-threatening condition called visceral leishmaniasis, characterized by the infection and consequent enormous swelling of internal organs such as liver and spleen. The disease type depends primarily on the *Leishmania* species infecting the host. Visceral leishmaniasis, which is fatal if not treated, is mostly caused by *L. donovani*.

Medicines currently available for leishmaniasis treatment are old, ineffective and/or mostly toxic to patients, who most times die from the treatment itself.



Courtesy to DNDi

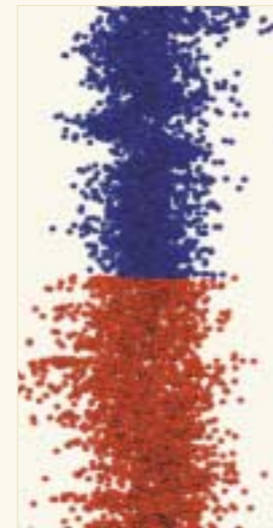


IP-Korea

The development of drugs able to treat visceral leishmaniasis has been a difficult task to achieve since the clinically relevant stage of the parasites, the amastigote, is hard to grow in large scale *in vitro*. We in IP-Korea, in partnership with Drugs for Neglected Diseases *initiative* (DNDi) have overcome this problem and are able to grow *L. donovani* inside human macrophages *in vitro*, in conditions as similar as possible to those found in natural infections in the human body. This cellular assay was adapted to high-throughput for automated image acquisition and we have just finished the screening of 200,000 compounds for visceral Leishmaniasis, which put IP-Korea in a leader and world-first position in the field.

In order to strength our *Leishmania* screening even further, we developed a secondary assay for kinetoplast-directed drug discovery. The kinetoplast is a unique single mitochondrion, exclusive to order Kinetoplastida (*Leishmania* and other parasites, such as *Trypanosoma cruzi*) and contains a number of excellent chemotherapeutic targets that are very unlikely to be found in the human host. The hits found in the HTS will be further tested in the kinetoplast assay for assessment of their potential kinetoplast-targeting mechanism of action.

- Throughput: 128,000 compounds/month;
- Unique visual cellular screening using the most relevant clinical specie *L. donovani* infecting human macrophage for more accurate selection of drug candidates;
- Dedicated in house developed software for automated result analysis.



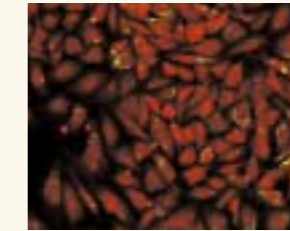
Chagas Disease

Chagas Disease is caused by the single-celled parasite *Trypanosoma cruzi* found in the Americas, where 18 million people are infected with the disease and other 120 million are at risk of contracting it. People affected are mostly the poor living in rural areas, although transmission can also happens through blood transfusion and accidental ingestion of the parasite.

Chagas Disease has a broad clinical manifestation, with two very distinctive phases: acute, characterized by very high fevers, and chronic, characterized by internal organs long-term damage, especially the heart and the gastrointestinal organs. The acute phase, when correctly diagnosed, can be treated, however there are no drugs available to treat the chronic phase of the disease, which persists over years and may finally leads to organ failure and death.



Courtesy to DNDi



IP-Korea

We are developing in close collaboration with Drugs for Neglected Diseases *initiative* (DNDi) a drug discovery program for Chagas Disease. We have developed the first phenotypic, image-based high-throughput screening available for the intracellular form of *T. cruzi* and in the following months we will perform 80,000 compounds screen, which will certainly lead to the discovery of new scaffolds that are able to inhibit the parasite growth inside human cells.

Chagas is a complex disease that is still poorly understood in its basic pathological mechanisms. To increase our knowledge about the disease and thus strength our drug discovery program, we also develop basic research in IP-Korea. In this aspect, we are the world first to perform a genome-wide small interference RNA (siRNA) for the discovery of human factors that play a role in the infection process and establishment of the disease. This approach involves intense collaboration between different groups in IP-Korea and consists of systematically knocking down the effect of a given gene in the Chagas Disease pathogenesis. The research on basic mechanisms of the disease will facilitate the discovery of future drug targets.

- Throughput: 224,000 compounds/month;
- Visual phenotypic automated screening for precise hit compounds selection;
- Combination of chemical compound screening drug candidates with human host cell genomic siRNA for target identification and mechanism of action determination;

