CHAGAS COLLABORATION AIMS TO TACKLE 'KISSING BUG' DISEASE

Researchers from Gunma University in Japan are working with colleagues in El Salvador to TACKLE THE PARASITIC AGENT behind a neglected tropical disease.

Researchers in Japan and El Salvador have identified plant-derived compounds that could treat Chagas disease, a vector-borne infectious illness, and are also working to unravel the mysterious mechanisms of this poorly understood affliction.

Listed as a neglected tropical disease by the World Health Organization (WHO), Chagas is a potentially fatal illness caused by the parasite *Trypanosoma cruzi*. The parasite is transmitted via blood-sucking insects known as triatomines, which often bite the face and are known as 'kissing bugs'. Humans and other mammals, can become infected when the bug's parasite-laden faeces come into contact with the wound.

▲ **Members of the project team from Gunma University, CICES, and the University of El Salvador.**

The disease triggers symptoms including fever, fatigue and swollen eyes, soon after infection. But in 30% of cases, this is much later followed by chronic symptoms, such as heart failure or gastrointestinal disorders, which cause disability or death. The chronic conditions only appear after a decade-long asymptomatic period, posing a great challenge for detection of the disease.

There are currently 6–7 million cases of Chagas disease worldwide, mostly in Latin America. Infection can also spread unnoticed via blood transfusions, organ transplants and from mothers to their children in utero. Medications used to treat it have strong side effects and need to be administered during the acute phase, after which there is no current treatment.

PLANT-BASED COMPOUNDS

The complex lifecycle of *T. cruzi* poses particular challenges to prevention and treatment. The parasite has three forms and transforms as it travels from insect to human host. The epimastigote form proliferates inside the kissing bug, then turns into trypomastigotes in the bloodstream and invades host cells. The final form, amastigotes, proliferate within host cells, transform to trypomastigotes again, then destroy human host cells and move to invade other cells.

Now, researchers from Gunma University in Maebashi and Keio University in Tokyo, Japan, and the National Scientific Research Center of El Salvador (CICES), and the University of El Salvador in San Salvador, led by parasitologist, Junko Nakajima-Shimada, and vice minister of education, Ricardo Cardona Alverenga, have found compounds in plants that might be new candidates for safe, effective medicines for all stages of the disease.

The researchers collected and screened 38 plant species native to El Salvador that were known to have anti-parasitic properties. An extract of the shrub *Piper jacquemontianum* used in traditional treatments for skin ailments looked particularly promising. However, the specific compound within the extract was unknown.

RESEARCHERS HOPE TO ESTABLISH ANIMAL MODELS OF CHAGAS DISEASE AT ACUTE AND CHRONIC PHASES.

The plant team separated each compound within the extract using silica gel column chromatography and obtained four substances. Of these substances, cardamomin exhibited the highest anti-parasitic effect on epimastigotes, halving their viability at concentrations of 66 micromoles per litre (μM).[1]

In another study, researchers from the Takasaki University of Health and Welfare developed a new compound with anti-parasitic effects on the two stages of *T. cruzi* that form inside a host's body.

They started by synthesizing a complex compound derived from the plant *Dracocephalum komarovii*, known to hinder the growth of trypomastigotes. They found that it was the quinone group attached to the compound that was responsible for anti-trypanosomal activity, rather than the entire compound.

As simple compounds are easier and cheaper to reproduce, they then synthesized more than 200 quinone-like compounds and tested them for anti-trypanosomal properties. Of these compounds, 21 were examined for the ability to cross cell membranes and solubility to assess their suitability as an oral drug. Eight demonstrated anti-parasitic effects on both trypomastigotes and amastigotes — one of those also showed promise as a potential oral drug.[2]

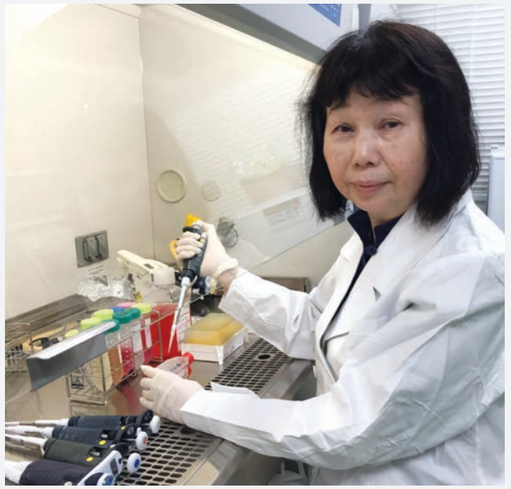
The researchers from Gunma University are now establishing in-vivo experiments in mice for the acute and chronic stages of the disease, and are seeking pharmaceutical partners for drug development.

CORNERING A CULPRIT

Understanding how Chagas disease works is another goal of the Japanese–El Salvadorian team. They want to know how exactly it progresses, why symptoms vary so widely and the reason for a long asymptomatic phase, as understanding all of this will aid treatment and prevention.

Researchers from Osaka Metropolitan University and the University of El Salvador (CENSALUD) are analysing the genes of one of six common types (Tc1) of *T. cruzi* in El Salvador, which is frequently linked to cardiac conditions. There are seven lineages and the chronic symptoms of Chagas disease vary between them. Their ultimate goal is to compare the genomes of the lineages and pinpoint the genetic basis of different symptoms associated with each type.

Furthermore, the researchers from Gunma University hope to establish animal models of the disease at both acute and chronic phases, which will allow them to monitor disease progress, track parasite development, and conduct clinical trials of new drugs. ■



▲ **Junko Nakajima-Shimada in her lab at Gunma University in Maebashi, Japan.**

MEANINGFUL COLLABORATIONS WITH THE DEVELOPING WORLD

The Japanese government's Science and Technology Research Partnership for Sustainable Development programme (SATREPS) supports collaborative research between Japan and developing countries to find solutions to global issues such as the management of disasters, the control of infectious diseases and food security.

A side-benefit of the Chagas disease collaboration has been helping to build national research capacity in El Salvador. Project leader, Junko Nakajima-Shimada of Gunma University, says that since there are few professionals able to perform PCR tests in the country, one of the local team members has been heavily involved with COVID-19 testing in El Salvador, thanks to expertise he developed in Japan prior to the pandemic. In return, young team members from Japan have had the opportunity to learn about another country's research challenges, and gained a valuable global perspective.

This collaborative work is in line with Gunma University's mission to play a globally active role, while contributing to the development of local communities.

University president, Yasuki Ishizaki, says it is his hope that the "research on Chagas disease will greatly contribute to the elucidation of the pathophysiology of the disease, speeding up the process of clinical drug development."

REFERENCES

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2. Suto, Y. et al., *Chemical and Pharmaceutical Bulletin* **69**, 1195–1199 (2021).

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