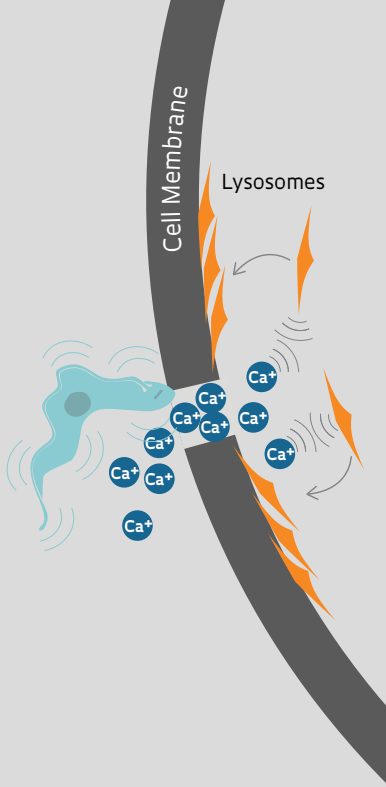


A promising forecast

Researchers count on the development of an effective Brazilian drug to combat Chagas disease in the medium term

Eduardo Geraque

A good candidate drug against century-old Chagas disease may appear within four years, in the optimistic view of researchers at the Center for Structural Molecular Biology (CeBiME) – one of the Research, Innovation and Dissemination Centers (RIDC) of the São Paulo Research Foundation (FAPESP).

"If an effective medication for Chagas disease is found one day, it will be made from 100% Brazilian technology," states Adriano Andricopulo, one of the coordinators of the University of São Paulo (USP) center in São Carlos.

Many obstacles lie along the way, and the fine results achieved in recent years are no guarantee that a drug will really come along any time soon.

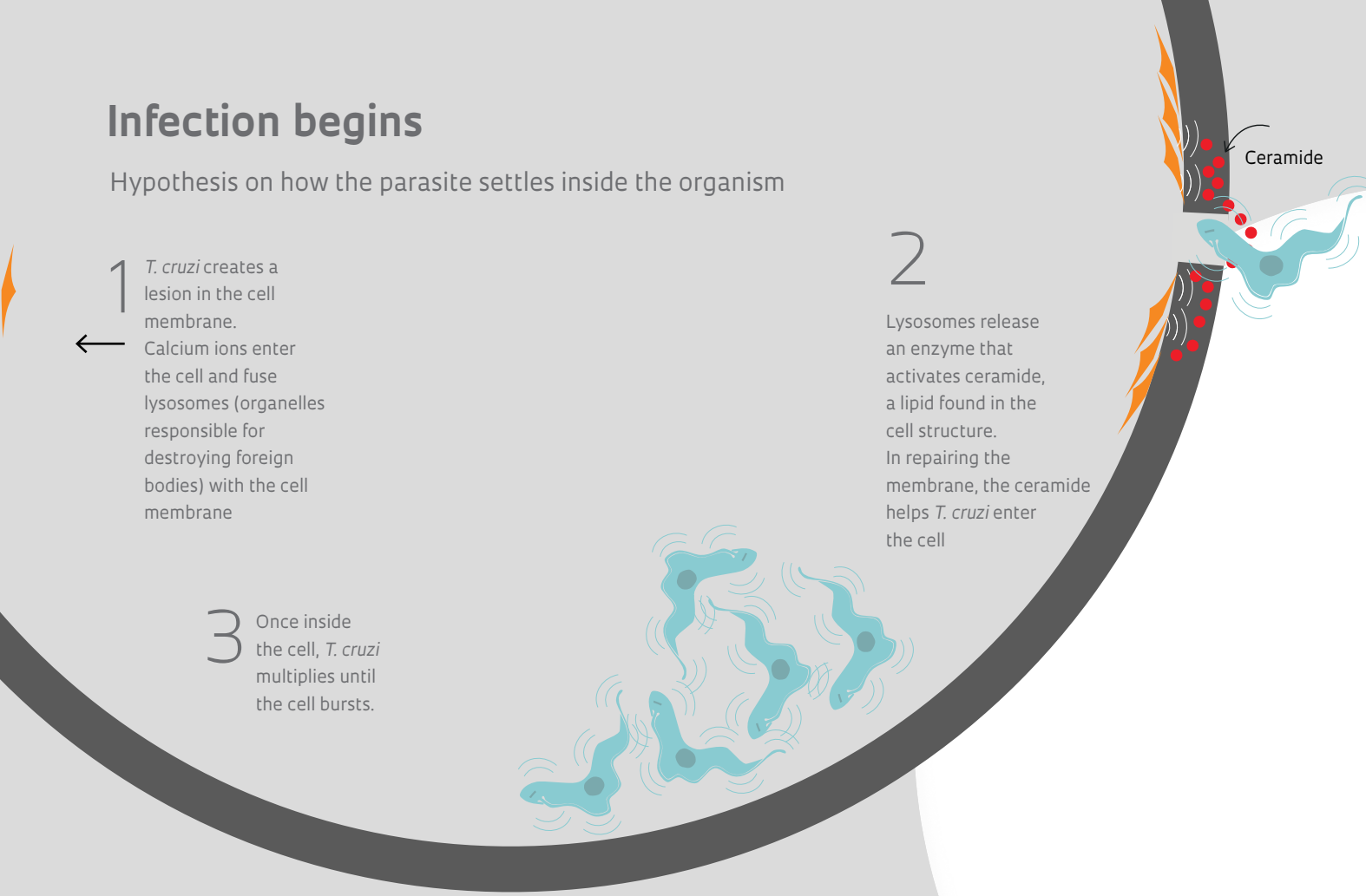
Although recent decades have seen many advances in biological knowledge of the problem, the behavior of *Trypanosoma cruzi* still presents significant challenges for scientists devoted to studying the illness.

The current stage of research into taming the parasite that causes Chagas disease reinforces the importance of conjoining basic science from structural molecular biology with applied science from medicinal chemistry, used in developing new drugs.

Not much progress has been recorded in the practical field since the 1970s, when molecular research began in earnest. Drugs have been discovered but so far are still considered quite toxic. Nor do the medicines now on the market serve for the chronic phase of the disease, the one that most concerns health sector leaders. Most patients today fall into this group.

Inside laboratories, work focuses on trying to identify the proteins that may be vital to proliferation of the disease. Once this stage has been understood, the effort will be to turn off the mechanism biochemically, which in practical terms may halt the infection caused by the parasite.

Among all the target proteins tested by the São Carlos team, cruzain (also known as cruzipain and cruzaine) seems the most promising to date. It is vitally important to *T. cruzi*. Research shows, for example, that this protein is involved in replication of the parasite. Using a chemical compound to disrupt the protein might prove to be an effective way of controlling the disease. Numbers from the World Health Organization



(WHO) indicate that 18 million people are currently infected with Chagas disease. Most of them live in Latin America.

Once basic research has shown that a candidate drug really reaches the target validated by researchers, new challenges can be overcome. From a clinical perspective, a drug must be absorbed, metabolized and distributed in the body in order to be used. It must act both at the molecular level and system-wide. In other words, it must truly kill *T. cruzi* – while not intoxicating the patient at the same time.

Molecular biology has played a prime role in research on Chagas disease since the 1970s, when important progress began to be made because research groups in São Paulo were paying markedly increased attention to the field. The purpose of concentrating more closely on the molecular level was to try to prevent the spread of protozoa inside host cells – in this case, within humans.

Research agencies like FAPESP started creating and incentivizing research projects and programs dedicated to the topic. Since then, the scientific results produced at laboratory benches in São Paulo can be divided into two large groups, according to physician Walter Colli, professor at the USP Chemistry Institute and one of the key players in the history of research on Chagas disease in Brazil over the past four decades.

"In Brazil, the molecular focus really got its start in the 1970s in São Paulo. *Trypanosoma cruzi* is a model for biological studies. The field of basic research saw a great deal of growth during the period. Even so, we are far from having a complete understanding of the biology of *T. cruzi*," the scientist states with conviction.

The endeavor to understand the relation between the parasite, as transmitting agent, and the host has yielded significant knowledge in basic research over the years, Colli says. Many skilled professionals have also been trained as a result, mainly in biochemistry and genomics. The more molecular approach to the issue replaced the morphological view that had predominated previously.

Colli's own group at the USP Chemistry Institute ended up contributing indirectly to the discovery of a new molecule, fully described in 1979. Doctoral candidate Maria Júlia Manso Alves arrived at this structure based on the group's find-

INFOGRAPHIC TIAGO CIRILLO

Scientist Carlos Chagas on the waters of the Negro River, on an expedition to the Amazon (1913)

ings. She showed that the form of *T. cruzi* was filled with sugars. Researcher Michael Ferguson, from Scotland, repeated the study and later informed the Brazilians that the properties of the protein anchors that he had begun to study greatly resembled those of the molecule described in Brazil. This intersecting information helped identify the anchors, which were glycolipid structures that attach proteins to the membranes.

Discoveries in the molecular field enjoyed even further growth once genomic techniques had become more firmly established, but paradoxically they have hampered progress in the second large group, that is, applied biology. Basic research has shown that *T. cruzi* is extremely complex, and fighting it inside the cell is therefore a major challenge.

One intriguing bit of information deciphered in recent decades, says Colli, is how the protozoan reads the information stored in its DNA. In most living beings, transcription – the process of making an RNA copy out of a DNA strand – is where genetic regulation takes place. But in the case of the causal agent of Chagas disease, studies conducted by a number of research groups – such as the team at the Paraná Molecular Biology Institute (IBMP), part of the Oswaldo Cruz Foundation (Fiocruz) – point to something different. Most *T. cruzi* gene regulation takes place after transcription, representing a new mechanism for protein synthesis from DNA.

Various groups agree that this important distinction between the protozoan and other living beings at the molecular level may be a powerful tool in accounting for a good part of the parasite's success in invading host cells.

Thoroughgoing research into the genetics of *T. cruzi*, researchers explain, may offer a substantial contribution to advances in applied biology research. Many argue that this path will in fact provide a substantial shortcut in the fight against the parasite and its invasive action.

Knowing that the system for reading DNA through protein synthesis is different in the protozoan responsible for Chagas disease and in humans is of utmost importance. Theoretically, drugs that interfere with one of the processes should not hamper the other.

Developing more suitable compounds – as the São Carlos group is attempting to do, for example – is the most viable pathway for the coming years, according to Colli, given advances in research into molecular genetics, a flourishing area in biological knowledge.

Another possibility – the development of Chagas vaccines – has been practically discarded by the scientific community. "It will not be possible to achieve 100% vaccination this way. There's the matter of logistics. For instance, who should get the vaccine? All 190 million Brazilians?"

Since transmission via the kissing bug (*barbeiro*) has all but ended, says Colli, there is no clearly defined target public for the vaccine.

T. cruzi has proven quite complex. This is why fighting it inside the cell is a major challenge

Today, active transmission occurs through ingestion of food contaminated by the feces of kissing bugs. For example, the most recent cases involved the consumption of sugarcane or açaí juice. But in this scenario, everyone would need to be vaccinated. "And there's also no way to measure the vaccine's efficacy."

If research into vaccines is meager (no scientific group devotes 100% of its time to the issue today), the development of new drugs is likewise quite complicated, as funds for this type of research are scarce.

Chagas is one of the so-called neglected diseases. Since most people with the illness are in poor countries or regions and lack the purchasing power to buy expensive medicines, the pharmaceutical industry does not invest heavily in this public health field.

Estimates are that it costs a company around one billion dollars to bring a drug to market. And it takes about twenty years to develop it. Then another ten years go by before there is any commercial return. Nobody, says Colli, is willing to take this on in the case of Chagas disease. In recent years, most applied biology research in this field has been sponsored by not-for-profit organizations that invest large sums of grant money.

The search for more effective drugs for adults is only part of the problem. Drugs that are safe for children, for example, are rare as well. But in terms of Latin America, the reality in many regions is that the disease is still transmitted in the traditional way, by the kissing bug. The worst situation is in Bolivia, where close to ten thousand new cases are reported every year. Even in Brazil, there are signs that the malady is settling in some regions of the Amazon.

The emergence of this disease was triggered by the movement of humans into vegetated areas, as occurred in the state of Minas Gerais.

The relation between parasite and host was discovered in the early twentieth century. In the remote town of Lassance, in the interior of Minas Gerais, physician Carlos Chagas (1879-1943) uncovered the mechanism of the disease that bears his name. He finished his study on April 14, 1909 (his scientific article is dated April 22 of that year), finalizing what is still considered the most important discovery ever made by a Brazilian scientist.

Unlike other illnesses transmitted by insects, such as dengue fever or malaria, it is not the bite of a transmitting insect that is the main culprit behind Chagas disease. The protozoan that causes the disease enters the human bloodstream through the bug's feces. When the victim scratches his skin, the contaminated feces enter the bite wound. *T. cruzi* lives inside the kissing bug's intestines. Once inside its human host, it mainly attacks vital organs, like the heart and liver.

The fact that the disease occurs in poor countries discourages investments in research for new drugs

The disease can be fatal in its acute phase. Or it can drag on for decades, afflicting its human victims with significant chronic problems. It doesn't always kill. The emblematic case of Berenice Soares de Moura illustrates this well. Carlos Chagas described the entire disease based on blood samples drawn from Berenice when she was two years old and living in a rural environment. She died of a stroke at the age of 74.

Estimates are that about 5 million Brazilians have Chagas disease today. In South America the figure totals 12 to 13 million. In the birthplace of the scientific discovery of Chagas disease, for example, hundreds of new cases are detected every year. This is not because of active transmission but rather because old cases are just beginning to surface now.

Once the disease cycle was known, the ways of combating it became fairly well delineated. It was clear that eliminating the kissing bug and thereby halting transmission would be the most efficacious way to stop the disease. Alternatively, another strategy for fighting Chagas disease might be to take advantage of the biology of the agents involved to keep the protozoan from exiting the insect's intestine and invading the human host's cells. ■

PROJECT

Center for Structural Molecular Biology (CeBiME) – No. 1998/14138-2 (2000-2012)

GRANT MECHANISM
Research Centers (RIDC) Program

COORDINATOR
Glaucius Oliva – IFSC/USP

INVESTMENT
R$28,449,954.27

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