PRESS RELEASE

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Subject line:
Discovering potential therapeutic protein inhibitors for Chagas disease through computational drug discovery and *in vitro* enzyme assays

(Tokyo, September 26) **Scientists at Tokyo Institute of Technology (Tokyo Tech), Nagasaki University have identified four potential protein inhibitors and unlocked drug discovery strategies for the treatment of Chagas disease by using advanced three-dimensional computer simulation by supercomputer TSUBAME in combination with *in vitro* experiments and X-ray crystallography. Through this "smart drug discovery" in which IT drug discovery and biochemical experiments cooperate, they identified hit compounds for target protein with a hit rate of 20 times or more than conventional High Throughput Screening (HTS) methods.**

Chagas disease is a potentially life-threatening illness caused by the parasite, *Trypanosoma cruzi*, and is transmitted to humans through triatomine blood-sucking bugs that are commonly referred to as “kissing bugs” or “vampire bugs”. While it was once confined to the Americas, worldwide travel has spread the disease, which is now endemic to approximately 20 countries. Currently, the World Health Organization (WHO) estimates that 10-13 million people are chronically infected, around 90 million people are exposed to the risk of the infection, and nearly 21,000 people die each year as a result, making effective treatment a necessity. Current treatments are largely effective in the first phase (acute) of the infection but have significantly diminished efficacy in the subsequent phase (chronic) of Chagas disease. Moreover, these drugs, which were developed in the 60s, are associated with severe adverse effects.

Masakazu Sekijima of Advanced Computational Drug Discovery Unit, at Tokyo Tech, Kiyoshi Kita of School of Tropical Medicine and Global Health at Nagasaki University and -colleagues used a multi-modal integrated approach to develop potential new anti-Chagas therapies by combining the principles of structure-based drug design, where therapy is designed with the knowledge of the target’s three-dimensional (3D) structure, with *in vitro* (colloquially referred to as “test tube experiments”) testing methods, and X-ray crystallography. This approach narrows the range of potential drug candidates more efficiently. Through virtual screening by TSUBAME at Tokyo Tech, one of the world's top, large-scale supercomputers, they selected their target protein, *T. cruzi* spermidine synthase, based on specific structural features and properties indicating its importance for survival in another *Trypanosoma* species. If the protein is required for survival of a species, inhibiting that protein could be a potential mechanism of action for a drug with activity against the parasite that causes Chagas disease.

They focused on Spermidine synthase (SpdSyn) as the target protein, as sourced from the iNTRODB system. This system was developed by Prof. Yutaka Akiyama, Prof. Takashi Ishida of Department of Computer Science, at Tokyo Tech, and Prof. Kiyoshi Kita of School of Tropical Medicine and Global Health at Nagasaki University. Detailed information regarding the search method is presented in Figure 1. The in-house web-system iNTRODB facilitates the selection of drug target proteins for NTDs, particularly for trypanosomiasis. This system provides information on trypanosomal proteins with useful annotations, including the protein structure from the Protein Data Bank (PDB) and the protein inhibitors from ChEMBL.

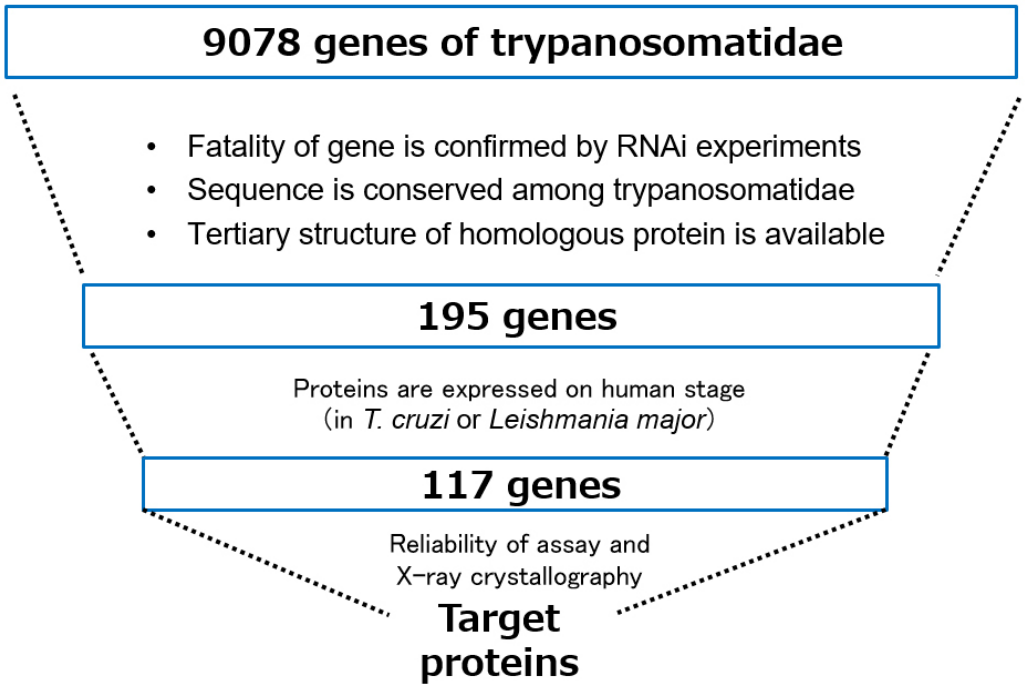

Figure 1. Search method for target proteins using iNTRODB.

Following selection, potential drug candidate inhibitors were identified through a screening search known as docking simulation—a structure-based drug design approach using 3D simulations to computationally match drug compounds to SpdSyn. They successfully identified four drug-like compounds that were virtual "matches" (referred to as "hits") then evaluated their inhibition activity *in vitro* and compared the results with those of a positive control. To further test potential activity and binding, they employed X-ray crystallography to confirm these four compounds in complex with the protein structure. Through interaction analyses for each compound the researchers found that all four compounds interacted with the proposed target binding sites through the same amino acid, Asp171. Additionally, molecular simulation suggested additional interacting sites for each compound that was not predicted by docking simulation.

Sekijima and team believe that their study's findings are indicative of the promise that docking simulation holds for the identification of potential drug-like inhibitors of the target protein and therapies for Chagas disease. They hope to demonstrate the general

applicability of their approach, opening doors to the discovery of treatments for other diseases.

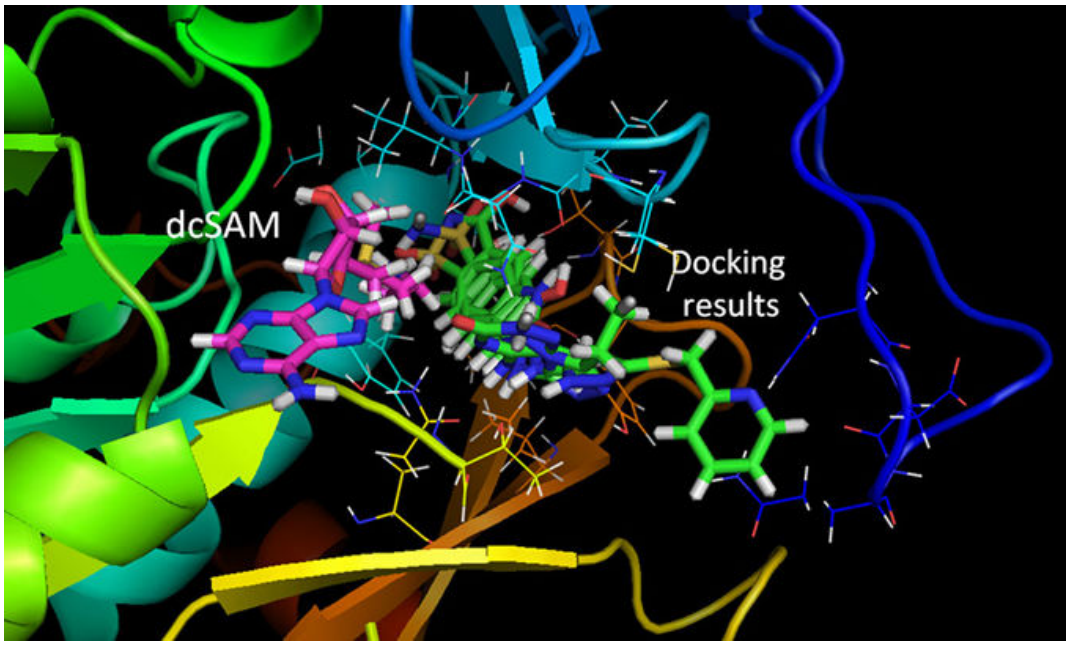

Figure 2. Results of the TcSpdSyn-ligand docking analysis.
This simulation was conducted with the *T. cruzi* SpdSyn X-ray structure (PDB ID code: 3BWC). The docking results show that all compounds bind to the putrescine-binding site and that dcSAM binding in its own site.

Reference

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Tokyo Institute of Technology stands at the forefront of research and higher education as the leading university for science and technology in Japan. Tokyo Tech researchers excel in a variety of fields, such as material science, biology, computer science and physics. Founded in 1881, Tokyo Tech has grown to host 10,000 undergraduate and graduate students who become principled leaders of their fields and some of the most sought-after scientists and engineers at top companies. Embodying the Japanese philosophy of "monotsukuri," meaning technical ingenuity and innovation, the Tokyo Tech community strives to make significant contributions to society through high-impact research.
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About Nagasaki University

In November 1857, a Dutch army surgeon JLC Pompe van Meerdervoort started medical lectures in Dutch to 12 students including Ryojyun Matsumoto, a Shogunate doctor. This medical school is the origin of the School of Medicine in Nagasaki University today and the university itself. Faculties of Education, Pharmaceutical Science, and Economics also celebrate 100 years of history. Experiencing the tragic event in 1945 when the atomic bomb dropped in Nagasaki city hit our students, teachers and staff members, a new Nagasaki University was created in May 1949 under the National School Establishment Law, merged with Higher School, Nagasaki Medical School, Teachers' School and others. The university currently has nine undergraduate faculties/schools and eight graduate schools for education and research, further expanding its scope to meet demands of the time.
Website: http://www.nagasaki-u.ac.jp/en/